# Maternal Gestational Diabetes Mellitus, Type 1 Diabetes, and Type 2 Diabetes During Pregnancy and Risk of ADHD in Offspring

*Anny H. Xiang,[1] Xinhui Wang,[1] Mayra P. Martinez,[1] Darios Getahun,[1] Kathleen A. Page,[2] Thomas A. Buchanan,[2] and Klara Feldman[3]*

*Diabetes Care 2018;41:2502–2508 | https://doi.org/10.2337/dc18-0733*




## OBJECTIVE

**To examine the relative importance of maternal preexisting type 1 diabetes (T1D), preexisting type 2 diabetes (T2D), and gestational diabetes mellitus (GDM) on risk of attention deficit/hyperactivity disorder (ADHD) in offspring.**

## RESEARCH DESIGN AND METHODS

**This retrospective birth cohort study included 333,182 singletons born in 1995–2012 within Kaiser Permanente Southern California hospitals. Children were prospectively followed through electronic medical records from age 4 years. Relative risks of ADHD associated with diabetes exposures in utero were estimated by hazard ratios (HRs) using Cox regression with adjustment for potential confounders. For GDM, timing of exposure was evaluated by gestational age at diagnosis and severity was assessed by the need for antidiabetes medication treatment during pregnancy.**

## RESULTS

**A total of 37,878 (11.4%) children were exposed to diabetes (522 exposed to T1D, 7,822 T2D, and 29,534 GDM). During a median of 4.9 years (interquartile range 2.2, 9.6) of follow-up after age 4 years, 17,415 (5.2%) children were diagnosed with ADHD. ADHD risk was not associated with GDM taken as a whole ($P = 0.50$) or with gestational age at GDM diagnosis ($P = 0.16$). However, the risk was significantly greater for the GDM requiring versus not requiring antidiabetes medications ($P < 0.001$). Compared with children unexposed to diabetes, the adjusted HRs for ADHD in children were 1.57 (95% CI 1.09–2.25) for exposure to T1D, 1.43 (1.29–1.60) for T2D, 1.26 (1.14–1.41) for GDM requiring antidiabetes medications, and 0.93 (0.86–1.01) for GDM not requiring medications.**

## CONCLUSIONS

**The hierarchy of risks suggests that severity of maternal diabetes (T1D vs. T2D vs. GDM requiring antidiabetes medications) influences the risk of ADHD in offspring of mothers with diabetes.**


Type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes mellitus (GDM) identified during pregnancy are the three main types of diabetes complicating pregnancy. It is increasingly recognized that exposure to maternal diabetes during pregnancy may increase the risk of neurobehavioral disorders in offspring (1–3), supporting the "fuel-mediated teratogenesis" hypothesis proposed by Norbert Freinkel three decades ago (4). Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental

*[1]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA*
*[2]Division of Endocrinology and Diabetes, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA*
*[3]Obstetrics and Gynecology, Kaiser Permanente Southern California, Pasadena, CA*

*Corresponding author: Anny H. Xiang, anny.h.xiang@kp.org.*

*Received 3 April 2018 and accepted 2 September 2018.*

*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0733/-/DC1.*

disorder with increasing prevalence in childhood (5,6). The disorder is highly prevalent, with an estimated prevalence of 5.3% worldwide in 2007 (7). The average age of diagnosis is 7 years (6). ADHD is characterized by inattention and/or hyperactivity-impulsivity that interferes with functioning or development. These characteristics can lead to unfavorable outcomes in academic performance, struggles with self-esteem, impairments in socialization, and susceptibility to accidents (8,9). As children and adolescents mature, the complications can be exacerbated and can lead to risky and addictive behavior such as substance use or abuse, video game addiction, and gambling (8,9). ADHD and its complications are not limited to the pediatric population; approximately one-third of ADHD cases diagnosed in childhood persist into adulthood (10). The direct and indirect impact of ADHD on quality of life generates a substantial burden to affected families, patients, and society (11). Prior research shows that genes and environmental factors and their interactions may contribute to the development of ADHD (11,12). Recent observations indicate that alterations in the intrauterine environment may play a role in the risk of ADHD (1,13).

Previous studies have examined the relationship of maternal T2D and GDM during pregnancy with risk of ADHD in offspring (14–17). All have had relatively small sample sizes (<155 T2D-exposed and <280 GDM-exposed children), and results have been inconsistent. Two recent large-sample European studies found that maternal history of T1D is associated with ADHD risk in children (18,19). However, no studies have assessed the relative importance of maternal T1D, T2D, and GDM or timing or severity of GDM during pregnancy on risk of ADHD in offspring. The purpose of this study is to examine the relative importance of these three main types of diabetes during pregnancy on risk of ADHD in offspring. Timing of exposure was assessed by gestational age at GDM diagnosis. Severity of GDM was assessed by the need for antidiabetes medication treatment during pregnancy.

## RESEARCH DESIGN AND METHODS

### Study Population

This longitudinal multiethnic cohort study included singleton children who were born at 28–44 weeks' gestation in Kaiser Permanente Southern California (KPSC) hospitals between 1 January 1995 and 31 December 2012. KPSC is a large health care organization that provides comprehensive care and uses an integrated electronic medical record (EMR) system. Demographic distribution of KPSC membership broadly represents Southern California residents (20). Per KPSC guidelines, children and adolescents <18 years of age who have signs, symptoms, or impairments suggestive of ADHD are administered one or more validated behavioral rating scales and referred to a behavior specialist for evaluation and diagnosis (21). The guidelines identify the Vanderbilt ADHD parent/teacher rating scales as the recommended structured, validated rating scales to use for initial evaluation (22,23). The guidelines further identify other behavioral rating scales such as the Conners Rating Scales, the Achenbach scales, the ADHD Rating Scale, and the Swanson, Nolan, and Pelham Questionnaire as validated scales that may be used in addition to the initial evaluation (5). The clinical practice guidelines from the American Academy of Pediatrics recommend that diagnosis, evaluation, and treatment of ADHD should start at age 4 years (24). For minimization of screening and ascertainment bias, children were required to be born at KPSC and enrolled in the KPSC health plan by age 4 years. Children were followed from age 4 years until the first date of the following: *1*) date of clinical diagnosis of ADHD, *2*) last date of continuous KPSC health plan membership, *3*) death from any cause, or *4*) 31 December 2017. Figure 1 depicts the derivation of the study cohort. All maternal and child data were extracted from EMR and birth certificate records and were linked by a unique membership identifier used for patient care. Data quality was assessed by means of data plots and frequency tables. Potential outliers and data errors were rectified by cross-checking against historical data in EMR. Validity of data was established in previous publications (2,5,13,25). The final study sample included a total of 333,182 children born to 243,882 individual mothers. The KPSC Institutional Review Board approved this study, with waiver of informed consent.

### Exposures and Outcomes

The primary exposure variables were maternal preexisting T1D, preexisting T2D, and GDM identified during pregnancy. A detailed description of the methods used to identify T2D and GDM has previously been published (2). Briefly, the diagnosis of maternal T2D antedating pregnancy was based on ICD-9 codes combined with glucose and $HbA_{1c}$ values and use of antidiabetes medications before the index pregnancy. The diagnosis of maternal GDM was based on laboratory glucose values from a 1-h 50-g glucose challenge test result ≥200 mg/dL or 3-h 100-g or 2-h 75-g oral glucose tolerance test during pregnancy with at least two abnormal plasma glucose values based on the Carpenter-Coustan thresholds (25,26). Gestational age at GDM diagnosis was calculated using date of the first glucose

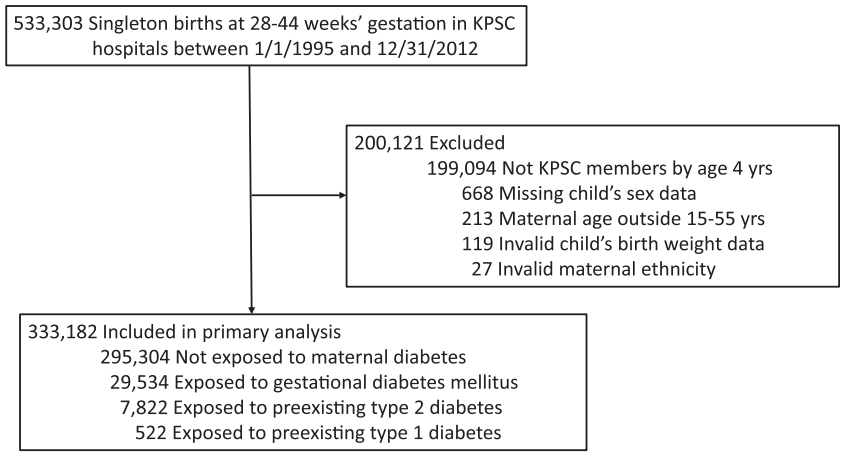


**Figure 1**—Study cohort derivation. yrs, years.

test that met the GDM diagnosis criteria, date of delivery, and gestational age at delivery available in the EMR. Data on antidiabetes medication (insulin or oral drugs such as glyburide and metformin) use during pregnancy were retrieved from the KPSC pharmacy dispensing records. Maternal T1D antedating pregnancy was identified using the algorithm developed for EMR data (27) and confirmed by insulin dispensed during pregnancy.

Main outcome measures were the presence or absence of ADHD and age at initial diagnosis or last follow-up. ADHD cases were identified based on ICD-9 codes 314.x or refills of ADHD-specific medications during the follow-up window from at least two separate visits. The validation and accuracy of these ADHD diagnostic codes have previously been checked (5,13).

### Covariates

Covariates to control for potential confounding were maternal age at delivery, parity, education, self-reported race/ethnicity, median family household income based on census tract of residence, maternal history of ADHD, history of medical comorbidity (cancer or $\geq$1 diagnoses of heart, lung, kidney, or liver disease), birth year, and sex of the child. In addition, potential confounding by smoking and alcohol use during pregnancy and maternal obesity was assessed. Maternal preeclampsia/eclampsia during pregnancy, gestational age at delivery, child's birth weight, and presence or absence of any birth defect might confound or mediate the diabetes exposure and thus were treated separately in data analysis.

### Statistical Analysis

Maternal and child characteristics were compared among unexposed, GDM, T2D, and T1D groups by $\chi^2$ test for proportions and ANOVA *F* test for means. Cumulative incidences of ADHD by exposure groups were estimated by the Kaplan-Meier method. Relative risks were estimated by hazard ratios (HRs) from Cox regression models. Family was specified as a random effect to control for potential correlation owing to multiple siblings born to the same mother. Birth year was included as a covariate to control for possible confounding owing to secular trends over time. Potential confounding owing to differences in maternal age, race/ethnicity, parity, education, household income, maternal history of ADHD, history of comorbidity, and sex of the child was assessed through covariate adjustment. The low percentage of children with missing covariate information on maternal parity, education, or household income was included in the multivariate-adjusted data analysis by inclusion of the category of "missing" for the missing data. Information on smoking and alcohol use during pregnancy and maternal prepregnancy BMI was available on 38% of the cohort because collection of these data electronically at KPSC did not start until October 2006. The missing indicator method was used to include all subjects in the multivariate-adjusted analysis with further adjustment for maternal smoking and alcohol use as well as maternal prepregnancy BMI. The missing indicator method is valid because these data were missing for administrative reasons and thus were missing completely at random. Smoking was treated as a categorical variable and prepregnancy BMI was treated as a continuous variable in the multivariate adjustment. Potential confounding or pathways associated with maternal preeclampsia/eclampsia, child's congenital anomalies, birth weight, and gestational age at delivery were assessed through additional adjustment for them as covariates in the models. Sensitivity analysis was conducted by exclusion of children with congenital anomalies.

SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC) and R 3.4.0 (64 bit) were used for data analysis. All statistical tests were two sided.

## RESULTS

Among the study sample of 333,182 children, 37,878 (11.4%) were exposed to maternal diabetes in utero, 522 to T1D, 7,822 to T2D, and 29,534 to GDM. The three diabetes-exposed groups and the unexposed group differed in maternal age, parity, education, household income, race/ethnicity, history of comorbidity, history of ADHD, preeclampsia/eclampsia, smoking during pregnancy, prepregnancy BMI, child's birth weight, gestational weeks at delivery, congenital anomalies, and child's sex (Table 1).

The 333,182 children were followed for a median of 4.9 years (interquartile range 2.2, 9.6) after age 4 years. During this time, 17,415 (5.2%) children were diagnosed with ADHD. Frequency of children with ADHD after exposure to T1D, T2D, GDM, or no diabetes was 9.2%, 6.2%, 4.8%, and 5.2%, respectively (*P* value for differences among groups $<$0.001). Among GDM cases, gestational age at GDM diagnosis was not associated with child's ADHD risk (bivariate $P = 0.10$), suggesting no clear window of vulnerability during pregnancy associated with child's ADHD risk. Regarding severity of GDM, 8,614 (29%) of the women with GDM were dispensed antidiabetes medication during pregnancy; 84% were dispensed insulin. Frequency of children with ADHD was 5.5% and 4.5% for the medication and no medication GDM groups, respectively ($P < 0.001$). The risk of ADHD in children was significantly greater for the GDM group with dispensed medication than for GDM without dispensed medication (bivariate HR 1.48 [95% CI 1.30–1.68], $P < 0.001$). Figure 2 depicts the crude cumulative incidences of ADHD by maternal diabetes exposure and GDM medication treatment. ADHD risk was greatest in children exposed to T1D, followed by those exposed to T2D and GDM with medication treatment. Interestingly, children of mothers with GDM who did not use medications had lower risk than the unexposed group.

After adjustment for birth year, risk of ADHD in children was significantly greater for those exposed to T1D and T2D but lower for those exposed to GDM taken as a whole than for children without diabetes exposure (Table 2, top, bivariate column). After adjustment for maternal age, race/ethnicity, parity, education, household income, maternal history of ADHD, history of comorbidity, and sex of the child, the ADHD risks remained significantly greater for T1D and T2D but comparable for GDM and no diabetes exposures (Table 2, top, multivariate column). The adjusted HRs were 1.56 (95% CI 1.09–2.25, $P = 0.02$) for T1D, 1.43 (1.28–1.59, $P < 0.001$) for T2D, and 1.02 (0.96–1.09, $P = 0.50$) for GDM (all compared with no diabetes exposure). Analysis directly comparing T1D with T2D exposure showed that, relative to T2D, the HR for T1D was 1.44 (1.00–2.06, $P = 0.05$) before and 1.16 (0.81–1.67, $P = 0.42$) after adjustment for potential confounders. Thus, potential confounders appeared to account for the majority of difference in ADHD risk between these two diabetes exposure groups. Gestational age at GDM diagnosis remained not significantly associated with child's ADHD risk (adjusted $P = 0.16$) and GDM with medication remained

**Table 1—Characteristics of the cohort at the time of the index pregnancy**

| | Diabetes exposure status | | | | |
|---|---|---|---|---|---|
| | Unexposed | GDM | Preexisting T1D | Preexisting T2D | *P** |
| *N* | 295,304 | 29,534 | 522 | 7,822 | |
| Maternal data | | | | | |
| Age (years) | | | | | <0.0001 |
| 15–19 | 16,471 (5.6) | 282 (1.0) | 17 (3.3) | 71 (0.9) | |
| 20–24 | 49,134 (16.6) | 2,049 (6.9) | 70 (13.4) | 463 (5.9) | |
| 25–29 | 88,354 (29.9) | 6,607 (22.4) | 143 (27.4) | 1,627 (20.8) | |
| 30–34 | 87,115 (29.5) | 10,310 (34.9) | 158 (30.3) | 2,708 (34.6) | |
| ≥35 | 54,230 (18.4) | 10,286 (34.8) | 134 (25.7) | 2,953 (37.8) | |
| Parity† | | | | | <0.0001 |
| 0 | 112,249 (39.1) | 9,937 (34.6) | 173 (34.4) | 2,459 (32.5) | |
| 1 | 97,319 (33.9) | 9,069 (31.5) | 181 (36.0) | 2,576 (34.1) | |
| ≥2 | 77,195 (26.9) | 9,747 (33.9) | 149 (29.6) | 2,520 (33.4) | |
| Education† | | | | | <0.0001 |
| ≤High school | 115,255 (39.6) | 11,533 (39.6) | 181 (35.4) | 2,815 (36.7) | |
| Some college | 84,142 (28.9) | 8,331 (28.6) | 176 (34.4) | 2,338 (30.5) | |
| ≥College graduate | 91,643 (31.5) | 9,289 (31.9) | 155 (30.3) | 2,521 (32.9) | |
| Household income† | | | | | <0.0001 |
| <$30,000 | 18,204 (6.6) | 1,755 (6.4) | 21 (4.5) | 597 (8.8) | |
| $30,000–$49,999 | 88,334 (32) | 9,088 (33.4) | 143 (30.4) | 2,346 (34.5) | |
| $50,000–$69,999 | 89,271 (32.4) | 9,010 (33.1) | 152 (32.3) | 2,132 (31.4) | |
| $70,000–$89,999 | 48,427 (17.6) | 4,571 (16.8) | 90 (19.1) | 1,073 (15.8) | |
| ≥$90,000 | 31,399 (11.4) | 2,820 (10.4) | 64 (13.6) | 646 (9.5) | |
| Race/ethnicity | | | | | <0.0001 |
| Non-Hispanic white | 79,944 (27.1) | 5,512 (18.7) | 211 (40.4) | 1,588 (20.3) | |
| Non-Hispanic black | 31,412 (10.6) | 2,216 (7.5) | 57 (10.9) | 747 (9.5) | |
| Hispanic | 145,388 (49.2) | 15,499 (52.5) | 210 (40.2) | 4,134 (52.9) | |
| Asian/Pacific islanders | 33,695 (11.4) | 5,759 (19.5) | 35 (6.7) | 1,182 (15.1) | |
| Others | 4,865 (1.6) | 548 (1.9) | 9 (1.7) | 171 (2.2) | |
| History of comorbidity | 26,944 (9.1) | 3,145 (10.6) | 86 (16.5) | 1,504 (19.2) | <0.0001 |
| History of ADHD | 5,316 (1.8) | 370 (1.3) | 15 (2.9) | 212 (2.7) | <0.0001 |
| Preeclampsia/eclampsia | 10,577 (3.6) | 1,571 (5.3) | 74 (14.2) | 600 (7.7) | <0.0001 |
| Child data | | | | | |
| Birth weight, g, mean (SD) | 3,388.2 (528.1) | 3,370.2 (584.1) | 3,480 (743.7) | 3,405.6 (673.0) | <0.0001 |
| Gestational weeks at birth, mean (SD) | 39.2 (1.7) | 38.6 (1.8) | 37.6 (2.1) | 38.3 (2.0) | <0.0001 |
| Congenital anomalies | 21,686 (7.3) | 2,609 (8.8) | 72 (13.8) | 927 (11.9) | <0.0001 |
| Female sex | 144,104 (48.8) | 14,198 (48.1) | 241 (46.2) | 3,777 (48.3) | 0.05 |

Data are *n* (%) unless otherwise indicated. **P* values are calculated from $\chi^2$ test for categorical variables and from ANOVA *F* test for continuous variables. †Numbers do not add up to the total owing to missingness.

associated with elevated ADHD risk compared with GDM without medication (adjusted HR 1.38 [95% CI 1.20–1.59], $P < 0.001$) after adjustment for potential confounders and each other.

Although GDM as a whole was not associated with child's ADHD risk, children exposed to GDM with medication treatment had significantly higher risk than the children in the no diabetes exposure group (adjusted HR 1.26 [95% CI 1.14–1.41], $P < 0.001$) (Table 2, bottom). The risk associated with exposure to GDM with medication was slightly lower than that observed for the T2D and T1D exposure groups. GDM without medication treatment had no greater risk than that for the no diabetes group.

The greater ADHD risks associated with maternal T1D, T2D, and GDM with medication treatment compared with no diabetes exposure remained significant after further adjustment for maternal smoking and alcohol use during pregnancy and prepregnancy BMI (Supplementary Table 1). Inclusion of covariates of preeclampsia/eclampsia at index pregnancy, presence or absence of congenital anomalies, birth weight, and gestational age at delivery had little impact on the HR estimates (Supplementary Table 1). Results from sensitivity analysis after exclusion of children with congenital anomalies were consistent with the results from the overall analysis (Supplementary Table 2).

## CONCLUSIONS

There are four novel findings from this large multiethnic birth cohort study regarding the relationship between maternal diabetes during pregnancy and risk of ADHD in children. First, children's exposure to GDM that required antidiabetes medication treatment during pregnancy was associated with 26% greater ADHD risk than compared with that in children without exposure to maternal diabetes. Second, compared with no diabetes exposure, T1D exposure carried the greatest risk (57%), followed by T2D (43%) and GDM requiring antidiabetes medication during pregnancy (26%). Third, GDM not requiring antidiabetes medication treatment during pregnancy had no increased risk. Lastly, the timing (early and late in gestation) of GDM diagnoses during pregnancy was not associated with ADHD risk. Thus, the hierarchy of risks that we observed suggests that severity of maternal

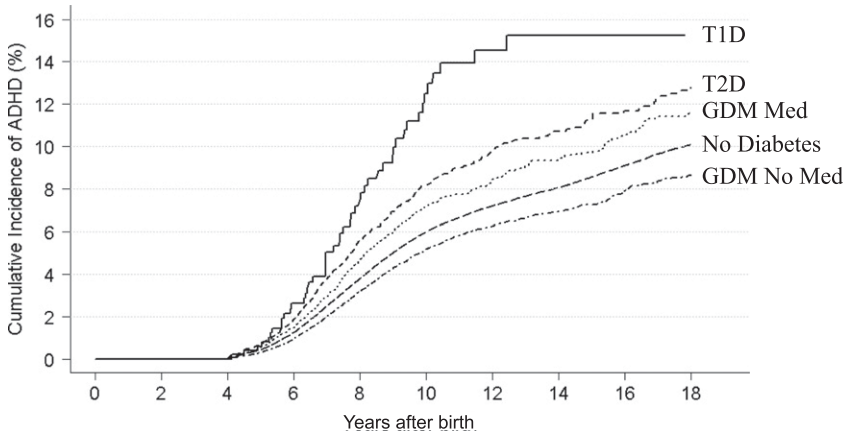


**Figure 2**—Crude cumulative incidence of ADHD by diabetes exposure in utero: preexisting T1D, preexisting T2D, GDM with dispensed antidiabetes medications during pregnancy (GDM Med), GDM without dispensed antidiabetes medications during pregnancy (GDM No Med), and no diabetes.

diabetes (T1D vs. T2D vs. GDM requiring antidiabetes medication) influences the risk of ADHD in offspring of mothers with diabetes.

Results from this large cohort provide valuable insight into the relationship between diabetic pregnancy and risk of ADHD in offspring. The comprehensive data with detailed information on pregestational and GDM diagnosis and medication use allowed us to evaluate GDM and preexisting T1D and T2D separately and to assess antidiabetes medication treatment and subsequently identify high-risk subgroups. Maternal GDM analyzed as a group was not associated with risk of ADHD in offspring after adjustment for potential confounders. However, the risk was elevated for the subgroup of GDM requiring medication treatment during pregnancy. This subgroup constituted 29% of the GDM group. Note that mothers with preexisting T1D and T2D were all dispensed antidiabetes medications during pregnancy. The majority of the mothers who required medication to manage diabetes during pregnancy were dispensed insulin (100% for T1D, 87% for T2D, and 84% for GDM requiring medication). Sensitivity analysis excluding individuals who received oral medications only had little impact on the results (Supplementary Table 3).

Future work is critically needed to assess whether levels of glycemic control may play a role in imparting risk of ADHD. Women with diabetes during pregnancy were given glucose meters and strips to measure glucose at home. Home glucose values were generally recorded in a paper log and reviewed at the next clinical visit with a health care provider. The self-measured glucose data were not entered in EMRs consistently or systematically for retrieval and analysis. Although $HbA_{1c}$ is generally not used to guide management of glycemic control during pregnancy, a subset of this cohort (91% of T1D, 65% of T2D, 63% of GDM requiring medication, 36% of GDM without medication, and 5.2% of no diabetes exposure) had laboratory $HbA_{1c}$ measured at any time during pregnancy. Supplementary Fig. 1 displays the sample sizes and mean $HbA_{1c}$ of these women by each trimester of pregnancy. During the first trimester, mean $HbA_{1c}$ levels in T1D, T2D, GDM with medication, GDM without medication, and nondiabetic pregnancies were 7.6% (60 mmol/mol), 6.8% (51 mmol/mol), 6.1% (43 mmol/mol), 5.6% (38 mmol/mol), and 5.4% (36 mmol/mol), respectively. This hierarchy was maintained throughout pregnancy, although differences were smaller in the second and third trimesters. Note that few women had longitudinal $HbA_{1c}$ for all trimesters and thus the $HbA_{1c}$ data are very limited and the subset may not be representative; therefore, results may be biased. Nonetheless, these data suggest that degree of glycemia control might play a role in explaining the risk. Future studies are needed to formally assess the relationship between glycemic control during pregnancy and ADHD risk in children.

A recent study from Sweden using national registry data reported that maternal T1D was associated with 35% greater risk of ADHD in offspring than in the general population (19). This study also showed that paternal T1D was associated with 20% greater risk of ADHD in



**Table 2—Associations between maternal diabetes and risk of ADHD in offspring**

| Maternal diabetes categories | No. with ADHD/total | Bivariate HR (95% CI)* | *P* | Multivariate-adjusted HR (95% CI)† | *P* |
|---|---|---|---|---|---|
| GDM considered overall as one group | | | | | |
| No diabetes | 15,469/295,304 | 1.00 (reference) | | 1.00 (reference) | |
| Preexisting T1D | 48/522 | 1.97 (1.39–2.79) | <0.001 | 1.56 (1.09–2.25) | 0.02 |
| Preexisting T2D | 485/7,822 | 1.40 (1.26–1.56) | <0.001 | 1.43 (1.28–1.59) | <0.001 |
| GDM | 1,413/29,534 | 0.94 (0.88–1.00) | 0.04 | 1.02 (0.96–1.09) | 0.50 |
| GDM separated by whether antidiabetes medication was used during pregnancy | | | | | |
| No diabetes | 15,469/295,304 | 1.00 (reference) | | 1.00 (reference) | |
| Preexisting T1D | 48/522 | 1.98 (1.40–2.81) | <0.001 | 1.57 (1.09–2.25) | 0.01 |
| Preexisting T2D | 485/7,822 | 1.41 (1.27–1.56) | <0.001 | 1.43 (1.29–1.60) | <0.001 |
| GDM with medication | 473/8,614 | 1.21 (1.09–1.33) | <0.001 | 1.26 (1.14–1.41) | <0.001 |
| GDM without medication | 940/20,920 | 0.84 (0.78–0.91) | <0.001 | 0.93 (0.86–1.01) | 0.07 |

*Adjusted for random sibling effect and birth year in the Cox regression models. †Adjusted for random sibling effect, birth year, maternal age at delivery, parity, education, household income, maternal race/ethnicity, history of comorbidity, history of maternal ADHD, and sex of the child in the Cox regression models.

offspring. Parental income and education levels were adjusted, suggesting that the elevated risk was not explained by socioeconomic status. The elevated risk associated with both paternal and maternal T1D suggests that genetic predisposition associated with immunity may play a role (18). The greater risk associated with maternal versus paternal T1D suggests that intrauterine glycemic environment also plays a role in the etiology of ADHD. Regarding T2D and GDM, one previous study with much smaller samples of children exposed to preexisting diabetes ($n$ = 153) or GDM ($n$ = 155) did not find associations between maternal diabetes and ADHD in children (Table 2 of ref. 17). Medication treatment effect was not assessed. An earlier study found that early school-age children born to mothers with preexisting diabetes ($n$ = 57) or GDM ($n$ = 32) had scores from neurobehavioral function tests that were indicative of ADHD compared with 57 matched control children born to mothers without diabetes (14). Of note, women with preexisting diabetes and GDM all had insulin treatment in that study (14). Two other studies found that ADHD risk associated with GDM was mostly observed in the subgroup with low socioeconomic status (15,16). However, only 21 children were exposed to GDM in one study (15) and 280 in the other study (16). GDM status was self-reported in both studies, and treatment information was not available in either study. It is possible that mothers with GDM and low socioeconomic status had more severe hyperglycemia that required medication to attempt glucose control during pregnancy. Taken together, these studies along with ours suggest that severe hyperglycemia that requires medication to manage diabetes during pregnancy, whether preexisting T1D or T2D or GDM, may be associated with increased ADHD risk in offspring.

Potential biological mechanisms linking ADHD risk in offspring and suboptimal glycemic environment during pregnancy are unknown and may involve multiple pathways. The majority of the medication users in our GDM group received insulin (84%), and 87% of those with preexisting T2D received insulin treatment during pregnancy. Importantly, insulin does not cross the placenta unless bound to antibodies (28), so direct effects of maternally administered insulin on fetal development are unlikely. Rather, women requiring antidiabetes medications during pregnancy may have relatively severe hyperglycemia that requires medication treatment to lower glucose levels. This hyperglycemia may predispose fetuses to stress, chronic inflammation, hypoxia, and fetal hyperinsulinemia, which in turn may interfere with fetal brain development during critical prenatal windows and lead to neurobehavioral disorders in later life (13,29–32). Epigenetics may be another potential mechanism (33). An animal study showed that chronic maternal hyperglycemia during pregnancy increased hippocampal excitement and altered behavior in offspring, and the effect appeared to be mediated by increased activation of the receptor for advanced glycation end products (RAGE)—a major source of inflammatory signaling in diabetes (34). The potential role of maternal hypoglycemia, which has been linked to altered brain function in adults (35), is unclear. Preexisting T2D or GDM is often accompanied by maternal obesity. Adjustment for maternal prepregnancy BMI did not affect the relative risk estimate associated with T1D and slightly reduced but did not eliminate the relative risk estimates associated with T2D and GDM requiring medication.

This study has several important strengths. To our knowledge, it is the first study to comprehensively evaluate ADHD risk associated with the three main types of diabetes complicating pregnancy and to assess severity of GDM based on need for antidiabetes medication treatment. This is by far the largest study of maternal diabetes and ADHD risk in offspring to date and includes data from multiple ethnicities. All data came from a single integrated clinical care system in which the demographics of the members are representative of Southern California residents (20). Children had to be born at KPSC and enrolled in the KPSC health plan by age 4 years with continued KPSC membership to minimize screening and ascertainment bias. Numerous confounding factors including sociodemographics, maternal history of ADHD, comorbidity, smoking, alcohol use during pregnancy, and maternal prepregnancy BMI were adjusted for. The validity of our data are further supported by the fact that our overall rate of 5.2% of children with ADHD diagnosis is comparable with the rate of the Centers for Disease Control and Prevention report: 5.9% of children age 4–11 years in the state of California had an ADHD diagnosis in 2011 (https://www.cdc.gov/ncbddd/adhd/prevalence.html). Our rate is slightly lower than the Centers for Disease Control and Prevention rate because children born in the last year for our cohort had not reached age 11 years yet. A preliminary analysis of diagnosing-physician ADHD specialty at the KPSC found 96% of children to have had ADHD diagnosed by professionals trained in diagnosis and treatment of the disorder, which highlights the greater validity of the ADHD diagnoses made at the KPSC relative to those based on parent-teacher reports or diagnoses made by untrained health care professionals (5).

We acknowledge some important limitations. Degree of glycemia control during pregnancy was not assessed because data were not readily available. Potential confounding owing to paternal risk factors could not be evaluated because of lack of data. Confounding bias due to potentially unmeasured intrauterine factors such as acetaminophen use (36), air pollution (37), and hypoglycemia; postnatal exposures such as head trauma; or genetic susceptibility could not be ruled out, although maternal history of ADHD was adjusted for in the data analysis. The etiology of ADHD is multifactorial, and factors that we haven't accounted for may explain the near-significant reduced risk of ADHD in those exposed to GDM without medication. Potential screening bias was not assessed, although screening for ADHD was not done specifically for a history of maternal diabetes. Medication adherence was not assessed. Potential confounding from smoking and alcohol use during pregnancy and maternal obesity may not be fully adjusted for owing to missing data for children born prior to October 2006. Whether neonatal and delivery characteristics such as types of delivery, neonatal distress, or hypoglycemia may confound or mediate the associations was not assessed and requires future investigation, although exclusion of children with congenital anomalies did not alter the results. Finally, this is an observational study, so causal inferences cannot be made.

In summary, data from this study show that the three main types of diabetes during pregnancy were associated with offspring ADHD risk in a hierarchical order. Compared with risk for no diabetes during

pregnancy, the risk was the greatest for T1D, followed by T2D and GDM requiring antidiabetes medication. GDM not requiring antidiabetes medication carried a risk that was comparable with that for no diabetes during pregnancy. Future studies are warranted to assess roles of glycemic control, potential causal factors and pathways, and approaches to mitigating ADHD risks.

**Acknowledgments.** The authors thank the patients of Kaiser Permanente for helping them improve care through the use of information collected through their electronic health record systems.

**Funding.** This work was partially supported by Kaiser Permanente Southern California Direct Community Benefit funds.

The funding agencies had no role in the design or conduct of the study, in the analysis or interpretation of data, or in the preparation, review, or approval of the manuscript.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** A.H.X. obtained funding. A.H.X. and X.W. were responsible for the study concept and design. A.H.X., X.W., and M.P.M. acquired data. A.H.X., X.W., M.P.M., D.G., K.A.P., T.A.B., and K.F. analyzed and interpreted data. A.H.X. drafted the manuscript. A.H.X., X.W., M.P.M., D.G., K.A.P., T.A.B., and K.F. revised the manuscript for important intellectual content. A.H.X. and X.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: congenital anomalies, genetic and epigenetic changes and developmental outcomes. Birth Defects Res C Embryo Today 2015;105:53–72
2. Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. JAMA 2015;313:1425–1434
3. Xiang AH, Wang X, Martinez MP, Page K, Buchanan TA, Feldman RK. Maternal type 1 diabetes and risk of autism in offspring. JAMA 2018;320:89–91
4. Freinkel N. Banting lecture 1980. Of pregnancy and progeny. Diabetes 1980;29:1023–1035
5. Getahun D, Jacobsen SJ, Fassett MJ, Chen W, Demissie K, Rhoads GG. Recent trends in childhood attention-deficit/hyperactivity disorder. JAMA Pediatr 2013;167:282–288
6. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry 2014;53:34–46.e2
7. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007;164:942–948
8. Bokor G, Anderson PD. Attention-deficit/hyperactivity disorder. J Pharm Pract 2014;27:336–349
9. Lahey BB, Lee SS, Sibley MH, Applegate B, Molina BSG, Pelham WE. Predictors of adolescent outcomes among 4-6-year-old children with attention-deficit/hyperactivity disorder. J Abnorm Psychol 2016;125:168–181
10. Barbaresi WJ, Colligan RC, Weaver AL, Voigt RG, Killian JM, Katusic SK. Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. Pediatrics 2013;131:637–644
11. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005;366:237–248
12. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 2013;54:3–16
13. Getahun D, Rhoads GG, Demissie K, et al. In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics 2013;131:e53–e61
14. Ornoy A, Ratzon N, Greenbaum C, Wolf A, Dulitzky M. School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. J Pediatr Endocrinol Metab 2001;14(Suppl. 1):681–689
15. Nomura Y, Marks DJ, Grossman B, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med 2012;166:337–343
16. Schmitt J, Romanos M. Prenatal and perinatal risk factors for attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2012;166:1074–1075
17. Li M, Fallin MD, Riley A, et al. The association of maternal obesity and diabetes with autism and other developmental disabilities. Pediatrics 2016;137:e20152206
18. Instanes JT, Halmoy A, Engeland A, Haavik J, Furu K, Klungsoyr K. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. Biol Psychiatry 2017;81:452–459
19. Ji J, Chen T, Sundquist J, Sundquist K. Type 1 diabetes in parents and risk of attention deficit/hyperactivity disorder in offspring: a population-based study in Sweden. Diabetes Care 2018;41:770–774
20. Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J 2012;16:37–41
21. Kaiser Permanente ADHD Guideline Development Team. *Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder in School-Age Children and Adolescents 2012 Clinical Practice Guideline*. Oakland, CA, Kaiser Permanente Care Management Institute, 2012
22. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2003;42:1015–1037
23. Wolraich ML, Lambert W, Doffing MA, Bickman L, Simmons T, Worley K. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. J Pediatr Psychol 2003;28:559–567
24. Wolraich M, Brown L, Brown RT, et al.; Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011;128:1007–1022
25. Xiang AH, Li BH, Black MH, et al. Racial and ethnic disparities in diabetes risk after gestational diabetes mellitus. Diabetologia 2011;54:3016–3021
26. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2004;27(Suppl. 1):S88–S90
27. Klompas M, Eggleston E, McVetta J, Lazarus R, Li L, Platt R. Automated detection and classification of type 1 versus type 2 diabetes using electronic health record data. Diabetes Care 2013;36:914–921
28. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC. Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus—its role in fetal macrosomia [published correction appears in N Engl J Med 1992;326:280]. N Engl J Med 1990;323:309–315
29. Ronald A, Pennell CE, Whitehouse AJ. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol 2011;1:223
30. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. J Psychiatry Neurosci 2008;33:395–404
31. Chen HJ, Lee YJ, Yeh GC, Lin HC. Association of attention-deficit/hyperactivity disorder with diabetes: a population-based study. Pediatr Res 2013;73:492–496
32. Khanh DV, Choi YH, Moh SH, Kinyua AW, Kim KW. Leptin and insulin signaling in dopaminergic neurons: relationship between energy balance and reward system. Front Psychol 2014;5:846
33. Archer T, Oscar-Berman M, Blum K. Epigenetics in developmental disorder: ADHD and endophenotypes. J Genet Syndr Gene Ther 2011;2:1000104
34. Chandna AR, Kuhlmann N, Bryce CA, Greba Q, Campanucci VA, Howland JG. Chronic maternal hyperglycemia induced during mid-pregnancy in rats increases RAGE expression, augments hippocampal excitability, and alters behavior of the offspring. Neuroscience 2015;303:241–260
35. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011;7:108–114
36. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014;168:313–320
37. Perera FP, Chang HW, Tang D, et al. Early-life exposure to polycyclic aromatic hydrocarbons and ADHD behavior problems. PLoS One 2014;9:e111670