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Authors

Zhu, Kexin

Wactawski-Wende, Jean

Mendola, Pauline

et al.

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Adverse pregnancy outcomes and risk of type 2 diabetes in postmenopausal women

Kexin Zhu, PhD,
Jean Wactawski-Wende, PhD,
Pauline Mendola, PhD,
Nisha I. Parikh, MD, MPH,
Michael J. LaMonte, PhD,
Vanessa M. Barnabei, MD,
Rachael Hageman Blair, PhD,
JoAnn E. Manson, MD, DrPH,
Simin Liu, MD, ScD,
Meng Wang, PhD,
Robert A. Wild, MD, PhD,
Aladdin H. Shadyab, PhD,
Linda Van Horn, PhD,
Erin S. Leblanc, MD,
Rachel Sinkey, MD,
Peter F. Schnatz, DO,
Nazmus Saquib, PhD,
Lina Mu, MD, PhD

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY (Drs Zhu, Wactawski-Wende, Mendola, LaMonte, Wang, and Mu); Division of Cardiovascular Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA (Dr Parikh); Department of Obstetrics and Gynecology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY (Dr Barnabei); Department of Biostatistics, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY (Dr Hageman Blair); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (Dr Manson); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (Dr Manson); Departments of Epidemiology, Medicine, and Surgery, Schools of Public Health and Medicine, Brown University, Providence, RI (Dr Liu); Departments of Obstetrics and Gynecology, Biostatistics and Clinical Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK (Dr Wild); Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA

Corresponding author: Lina Mu, MD, PhD. linamu@buffalo.edu.

The authors report no conflict of interest.

(Dr Shadyab); Department of Preventive Medicine, North-western University Feinberg School of Medicine, Chicago, IL (Dr Van Horn); Kaiser Permanente, Center for Health Research, Portland, OR (Dr Leblanc); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL (Dr Sinkey); Department of Obstetrics and Gynecology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA (Dr Schnatz); and Department of Research, College of Medicine, Sulaiman Al Rajhi University, Al Bukayriah, Kingdom of Saudi Arabia (Dr Saquib).

Abstract

BACKGROUND: Although gestational diabetes mellitus and delivering high-birthweight infants are known to predict a higher risk of future type 2 diabetes mellitus, the association of hypertensive disorders of pregnancy and other adverse pregnancy outcomes with type 2 diabetes mellitus is not well established.

OBJECTIVE: This study aimed to examine the associations between different types of adverse pregnancy outcomes and incident type 2 diabetes mellitus among postmenopausal women.

STUDY DESIGN: The Women's Health Initiative, a nationwide cohort of postmenopausal women, collected self-reported history of adverse pregnancy outcomes, including gestational diabetes mellitus, hypertensive disorders of pregnancy, preterm birth, and delivering low-birthweight (<2500 g) or high-birthweight (>4500 g) infants. Participants were followed up annually for self-reported incident type 2 diabetes mellitus treated with medication from baseline (1993–1998) to March 2021. This study used logistic regression to examine the associations of any and individual adverse pregnancy outcomes with diabetes mellitus. Stratified analyses were performed to assess effect modification by body mass index, race and ethnicity, education, parity, breastfeeding, and age at first birth.

RESULTS: This analysis included 49,717 women without a history of diabetes mellitus at enrollment who had a least 1 pregnancy and responded to the questionnaire about adverse pregnancy outcomes. After adjusting for body mass index, demographic, lifestyle, and reproductive factors, gestational diabetes mellitus (odds ratio, 2.26; 95% confidence interval, 1.94–2.63), high birthweight (odds ratio, 1.30; 95% confidence interval, 1.18–1.44), and hypertensive disorders of pregnancy (odds ratio, 1.18; 95% confidence interval, 1.08–1.30) were independently associated with higher odds of type 2 diabetes mellitus, whereas preterm birth and low birthweight were not associated with diabetes mellitus risk. A history of ≥2 adverse pregnancy outcomes was associated with higher odds of type 2 diabetes mellitus (odds ratio, 1.55; 95% confidence interval, 1.28–1.88). This study further observed higher odds of type 2 diabetes mellitus (odds ratio, 3.69; 95% confidence interval, 2.38–5.70) among women with a history of both gestational diabetes mellitus and hypertensive disorders of pregnancy than those without any adverse pregnancy outcomes.

CONCLUSION: Postmenopausal women with a history of gestational diabetes mellitus, those delivering high-birthweight infants, or those with hypertensive disorders of pregnancy are at risk of future type 2 diabetes mellitus. In addition, women with ≥2 conditions had an augmented risk and might be prioritized for screening and prevention efforts for type 2 diabetes mellitus.

Keywords

diabetes mellitus; gestational diabetes mellitus; high birthweight; hypertensive disorders of pregnancy

Introduction

Pregnancy requires substantial vascular, metabolic, and physiological adaptation and is associated with considerable changes in lipid profile and an increase in insulin resistance.[1,2] Women who have marked metabolic and vascular challenges of pregnancy may develop adverse pregnancy outcomes (APOs), including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), preterm birth (PTB), and delivering infants with abnormal birthweight. The development of APOs may unmask preexisting metabolic risks through the stress of pregnancy and may alter women's trajectory toward developing chronic diseases.[3–9]

Type 2 diabetes mellitus (T2D) is a complex and severe metabolic disease and can affect an individual's functional capacity and quality of life.[10–12] Approximately 24% of American adults aged ≥65 were diagnosed with T2D in 2017–2020.[13] Although the prevalence of T2D was higher in men,[14] women are more severely affected by diabetes mellituserelated complications and death.[11,15–17] Accumulating evidence suggests that APOs might be associated with a higher risk of developing T2D.[18–21] Although the association of GDM with T2D is well established,[22] the risk of T2D among women with GDM and other APOs is less studied. Some studies have reported the association of HDP with T2D, but most assessed the T2D risk within 2 decades after delivery, and many did not account for important confounders (eg, diet or physical activity).[23] Research investigating other APOs, such as PTB or low birthweight (LBW), is limited.[18,19,24,25] Moreover, several APOs may occur in the same woman, although limited studies have examined the association of coexisting APOs with T2D risk.[26]

Body mass index (BMI) is a well-established, modifiable risk factor for T2D. It is unclear whether the effect of APOs on T2D risk differs by BMI.[19] Racial and ethnic disparities in the prevalence of APOs exist in the United States, with non-Hispanic Black and Hispanic mothers being more afflicted by PTB and LBW delivery[27] and non-Hispanic Asian women more affected by GDM.[28] Socioeconomic disparities have been observed in the prevalence of both APOs[29–31] and T2D.[32] Investigating the association between APOs and T2D by factors related to disparities in T2D is warranted to identify populations with higher vulnerability to later life health consequences of APOs. Reproductive factors, such as parity and breastfeeding, are associated with T2D risk,[33–36] and these factors could potentially modify the APO-T2D associations via some biological pathways, including insulin sensitivity and glucose metabolism.[37,38]

This study aimed to investigate the association between a history of APOs and the risk of T2D in postmenopausal women and to explore whether the associations are modified by BMI, race, ethnicity, education, parity, breastfeeding, and age at first birth.

Materials and Methods

Study population

The Women's Health Initiative (WHI) is a nationwide study involving 3 clinical trials (CTs; hormone therapy, dietary modification, and calcium and vitamin D supplementation) and an observational study (OS).[39–41] A total of 161,808 women aged 50 to 79 years were recruited at 40 clinical centers throughout the United States between 1993 and 1998 and followed up prospectively.[39–41] The WHI study was approved by institutional review boards at all 40 clinical centers, and all participants provided written informed consent.

Although extensive data were collected during clinical examinations and interviews at WHI enrollment, APO history was not assessed at baseline. In 2017, 79,104 of 161,808 women enrolled in the WHI who were still being followed up were mailed a survey about their history of APOs,[9,42] and 58,274 of 79,104 women (74%) responded to that survey. We excluded those who were never pregnant (n=6492), those who did not answer any APO questions (n=1175), or those with a history of T2D at WHI enrollment (n=890), resulting in 49,717 women in the current analysis (Figure 1). Women with a history of T2D at enrollment were excluded from the primary analysis because we could not determine whether T2D occurred before or after APOs.

Exposure measurement

Of note, 6 APOs were assessed on the survey, including PTB (<37 weeks of gestation), preeclampsia (PE), gestational hypertension (GH), GDM, LBW (<5.5 lb [2500 g]), and high birthweight (HBW; >9 lb 14 oz [4500 g]).On the survey, 3 options included "no," "yes," and "do not know." We grouped women who responded "yes" to GH and/or PE questions into a single category of HDP.[9,42]

Outcome measurement

Baseline T2D was assessed by asking participants "Did a doctor ever say that you had sugar diabetes or high blood sugar when you were not pregnant?" Incident T2D diagnosis was self-reported on annually mailed questionnaires through March 2021. The case-finding question reads "Since the date given on the front of this form, has a doctor prescribed any of the following pills or treatments?" Choices included "pills for diabetes" and "insulin shots for diabetes." Self-reported T2D treated with medication in the WHI is a reliable and valid indicator of diagnosed diabetes mellitus based on medication inventories, fasting glucose levels, and medical record review.[43–45]

Covariate measurement

In the baseline questionnaires, participants self-reported demographic information (age, race and ethnicity, education, and annual family income), lifestyle factors (diet, smoking, and alcohol intake), personal and family medical history, and reproductive history (parity, breastfeeding, age at first birth, menarche, and menopause). Using standardized protocols, height and weight were obtained at the baseline clinic visit by trained WHI staff. BMI was calculated as weight divided by height squared. Physical activity was measured by the validated WHI physical activity questionnaire.[46] The Alternative Healthy Eating Index

(AHEI)-2010 score was computed on the basis of 11 dietary components from a baseline food frequency questionnaire.[47–49]

Statistical analysis

We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of T2D associated with any APO and with each APO exposure separately, using "no" responses as the referent group. Women with "do not know" or missing responses were excluded from the primary analysis (1.5%–7.8% according to different APO exposures). To assess potential confounders, the change-in-estimate method was used to evaluate each covariate for each APO with T2D. For each APO, we added each covariate one at a time to the crude model. In the main model, we adjusted for demographics and covariates that changed the unadjusted estimate by ≥10% for at least 2 APOs, including BMI at enrollment (continuous), physical activity (continuous), age at menarche (≤11, 12–13, and ≥14), parity (0–1, 2, 3, 4, and ≥5), age at first birth (never had term pregnancy, <20, 20–29, and ≥30), and age at menopause (continuous). In fully adjusted models, we additionally adjusted for covariates that changed the unadjusted estimate by ≥10% for any APO, including AHEI-2010 (continuous), smoking status (never, past, and current), pack-years of smoking (never, 5, 5–19, and ≥20 cigarettes/day), alcohol intake (never, past, <7, and ≥7 drinks/week), regularity of periods (no, yes, and sometimes regular and sometimes irregular), breastfeeding (no or yes), and family history of diabetes mellitus (no or yes). Moreover, the region at WHI enrollment, study component (CT and OS), and CT randomization arm were included in fully adjusted models. We further adjusted for all APOs simultaneously to control for potential confounding by having more than 1 APO. In addition, we examined the association of multiple APOs with T2D, and women without any APOs served as the referent group. We did not find multicollinearity of covariates as all the variance inflation factors were <5.

To explore potential effect modification, we performed stratified analyses by BMI (<25.0, 25.0–29.9, and ≥30.0 kg/m^2), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), education (high school and below and college and above), parity (0–2 and >2), breastfeeding (no or yes), and age at first birth (<30 and ≥30 years). A product term defined by the APO exposure of interest and each potential effect modifier was included in the multivariable regression models, and the significance of interaction terms was assessed by the Wald tests. Benjamini-Hochberg adjustment was made to account for multiple comparisons.[50]

In the sensitivity analyses, first, we included women with the "do not know" responses in the models, in which the "do not know" responses were (1) treated as a separate category, (2) combined with "no" responses, or (3) combined with "yes" responses. Second, we excluded women with a history of atherosclerotic cardiovascular disease at enrollment (n=1410; myocardial infarction, coronary revascularization, stroke, and congestive heart failure) because the treatment of these diseases might affect T2D risk. Third, missing data in covariates were imputed by chained equations algorithm using the R package "mice,"[51] and 10 rounds of multiple imputations were performed. Fourth, we included women with T2D at WHI enrollment in the analysis (n=890).

Results

Of 49,717 women, 10,893 (21.9%) reported newly diagnosed and treated T2D during follow-up, and 14,297 (28.8%) reported a history of having at least 1 APO. The prevalence of having a history of GDM, HBW, HDP, PTB, and LBW were 1.9%, 5.8%, 6.3%, 14.7%, and 12.5%, respectively (Supplemental Table 1). Compared with those without any APOs, women who reported having one or more APOs were more likely to have lower levels of education and annual family income, be non-White, have higher BMI, have lower physical activity, have poorer AHEI-2010 scores, be current smokers, have a younger age at menarche, have a greater frequency of having had irregular periods, have higher parity, and have a family history of diabetes mellitus (Table 1). Baseline characteristics by the status of each APO are presented in Supplemental Table 2.

A history of any APO was associated with higher odds of T2D (OR, 1.19; 95% CI, 1.13–1.26), after adjusting for age, race and ethnicity, education, annual family income, BMI, physical activity, age at menarche, parity, age at first birth, and age at menopause (Table 2). Women with a history of GDM (OR, 2.26; 95% CI, 1.94–2.63), HBW (OR, 1.30; 95% CI, 1.18–1.44), and HDP (OR, 1.18; 95% CI, 1.08–1.30) had higher odds of T2D than those without the corresponding APO, respectively. However, we did not observe significant associations for PTB (OR, 1.06; 95% CI, 0.99–1.13) or LBW (OR, 1.02; 95% CI, 0.95–1.10). The results were consistent in the fully adjusted models and after simultaneously adjusting for all APOs.

A history of an increased number of APOs was associated with higher odds of T2D (1–2 APOs: OR, 1.13; 95% CI, 1.06–1.20; >2 APOs: OR, 1.55; 95% CI, 1.28–1.88; *P* value for trend<.0001) (Table 2). In addition, the odds of T2D were higher among women reporting having GDM and any other APOs than among those without any APOs (OR, 2.65; 95% CI, 2.12–3.30) (Figure 2). The T2D risk was higher among women with a history of both GDM and HDP (OR, 3.69; 95% CI, 2.38–5.70), GDM and HBW (OR, 2.23; 95% CI, 1.41–3.52), or GDM and PTB (OR, 3.41; 95% CI, 1.67–6.96) than those with GDM only (OR, 2.04; 95% CI, 1.59–2.62).

In the stratified analysis (Table 3), we observed an interaction between parity and GDM on T2D (*P* values for interaction=.006). The associations were stronger among women with >2 parity (OR, 2.54; 95% CI, 2.08–3.12) than among women with 0 to 2 parity (OR, 1.52; 95% CI, 1.11–2.08). The associations between any APO and T2D were stronger among non-Hispanic Black women (OR, 1.53; 95% CI, 1.21–1.93) than among non-Hispanic White (OR, 1.19; 95% CI, 1.12–1.26), Hispanic (OR, 0.93; 95% CI, 0.66–1.30), or other races (OR, 1.18; 95% CI, 0.89–1.57) (*P* values for interaction=.036). We did not observe effect modification by BMI at enrollment, education, breastfeeding, or age at first birth. None of the interaction terms were statistically significant after multiple comparisons adjustment.

The results remained consistent in the sensitivity analyses (Supplemental Tables 3 and 4).

Comment

Principal findings

In this cohort of 49,717 postmenopausal women, a history of GDM, HBW, and HDP were each associated with an increased risk of incident T2D diagnosis in later life. Women with a history of ≥2 APOs had an augmented risk.

Results in the context of what is known

GDM results from impaired glucose tolerance and β-cell dysfunction during pregnancy.[52,53] It is biologically plausible that women with GDM have a higher susceptibility to later T2D as GDM and T2D share common risk factors, including physical inactivity and obesity.[52,54] Although GDM often resolves after delivery, some degree of underlying insulin resistance and β-cell dysfunction might persist beyond pregnancy. Our study showed a 2.65-fold increased odds of T2D among women with a history of GDM; however, the magnitude of this association was smaller in our study than other studies[20,22,55–57] Wang et al[55] reported that women experiencing GDM have a 6.52-fold (95% CI, 5.73–7.43) higher risk of T2D than women without GDM using medical records in Louisiana in 1990–2009. Our findings might be somewhat different from those in other studies because of the differences in the assessment of GDM, its low prevalence several decades ago, and differences in the study populations. Most of our participants were pregnant between the 1940s and 1970s, when standardized screening and diagnostic criteria for GDM were not established,[58] suggesting many women in our study might have unscreened and undiagnosed GDM. Only 1.9% of women in our study self-reported a history of GDM, which was comparable with that in the National Collaborative Perinatal Project in 1959–1965 (1.7%).[59] However, the GDM prevalence in our study was much lower than the current prevalence reported by Wang et al[55] (5.7%). An increase in maternal age and elevated obesity prevalence among women of childbearing age in the last few decades have also contributed to the temporal changes in the prevalence of GDM.[60,61] In addition, women in our study might fail to recall their diagnosis of GDM 3 to 4 decades earlier. We only included WHI participants who survived to 2017, which could introduce survival bias and potentially attenuate associations. Last, our participants were predominately non-Hispanic White (89.0%), whose T2D risk after GDM tends to be lower than other racial and ethnic groups.[55,56]

Consistent with previous studies,[18,62–64] women delivering HBW infants had an increased T2D risk, irrespective of reported GDM and other APOs. HBW infants might serve as an indicator of maternal hyperglycemia despite not being diagnosed with GDM or not being screened or detected for GDM.[18,65] In addition, HBW infants might uncover other risk factors, including prepregnancy obesity.[66] The positive association of HDP with T2D found in our study was in line with previous research.[23] HDP shares some preexisting risk factors for T2D, such as obesity and insulin resistance.[67–69] HDP may be an earlier manifestation of underlying insulin resistance brought out by the increased metabolic demands of pregnancy, which may continue or even worsen after pregnancy.[70,71] PE represents a more severe condition than GH, and PE was associated with higher odds of T2D than GH in previous research.[4,72,73] However, in our study, a history of GH presented a stronger association with T2D (OR, 1.30; 95% CI, 1.15–1.48) than PE (OR, 1.13; 95% CI, 1.01–1.27), which

may be due to misclassification of GH and PE because of self-reported data, recall bias, and changes in the diagnostic criteria. We did not have data on the severity of PE either. Future studies with validated types of HDP may explore whether their effects on future T2D risk are different. In addition, we found that the coexisting GDM and HDP presented a higher T2D risk than GDM alone. Moreover, women with GDM are at increased risk of HDP,[74] and pregnancies with both complications might suggest a more severe state of pathophysiological changes, predisposing to subsequent T2D in later life. However, these findings may be due to chance because the confidence intervals overlap.

Inconsistent with other studies,[18,19,24,75] we did not observe an association of PTB or LBW with T2D. In the Nurses' Health Study, T2D risk increased by 17% for women who delivered their first infant before term compared with those who delivered at term.[75] The associations were the strongest in the first 10 years after delivery, attenuated over follow-up, and were only significant for very PTB (<32 weeks of gestation) after a 20-year follow-up.[75] However, in our study, women were followed up for more than 25 years, and we did not have information on subcategories of PTB; moreover, we excluded those who had T2D at baseline and so would not have captured women with T2D within 10 years of delivery. Interestingly, we found that women with a history of both GDM and PTB presented a stronger T2D risk than those reporting having only GDM. PTB was found more prevalent in patients with poor glycemic control[76]; women with GDM who delivered preterm might have had increased severity of glucose intolerance and be more likely to develop T2D after pregnancy. However, our results could also be due to chance, given the small number of women who reported both complications (n=36).

Our study suggested a potential interaction of GDM and parity in the development of T2D. Multiparous women were more likely to have recurrent GDM,[77] long-term weight gain,[78] and impaired glucose homeostasis, posing a greater risk of future T2D.[79] However, our results could be due to chance given that the interaction terms were not statistically significant after multiple comparisons tests.

Clinical implications

Although the American Diabetes Association recommends screening women with GDM at 4 to 12 weeks after delivery and every 1 to 3 years thereafter for T2D,[80] the attendance for postpartum screening is poor,[81–83] and healthcare providers have not fully implemented screening guidelines.[84] Our findings may help raise providers' awareness in implementing the screening protocols, not only among women who have experienced GDM or delivered HBW infants but also among women with a history of HDP. In addition, a history of ≥2 APOs may present as an important risk factor while evaluating T2D risk even for women in their 60s and beyond.

Research implications

The association of delivering premature or LBW infants with a mother's T2D risk merits further investigation. Although we investigated the association of coexisting APOs with T2D risk, we could not differentiate whether multiple APOs occurred in the same or recurrent

pregnancies. More research is needed to understand the combined effects of APOs on T2D risk.

Strengths and limitations

The strengths of this study include the use of a large, nationwide cohort of older women who have been followed up annually for more than 25 years, which allowed sufficient time for a substantial proportion of participants to develop T2D. In addition, the detailed information on lifestyle and reproductive factors available in the WHI allowed us to account for a set of confounders.

Several limitations should be considered. First, survival bias cannot be ruled out as we were only able to include WHI participants who had survived to 2017 and responded to questions on APOs. Women with a history of APOs and those who were at a higher risk of T2D might have died before the survey (Supplemental Table 5), which could bias our results toward the null. Second, women with prevalent T2D were excluded at baseline, possibly resulting in a metabolically healthier cohort. Third, relying on the self-reported history of APOs occurring 3 to 4 decades earlier by postmenopausal women could introduce recall bias, as those with T2D may be more likely to recall having a history of APOs. Fourth, self-reported information on confounders might result in residual confounding. In addition, we only adjusted for potential confounders collected at WHI baseline and did not consider their changes over the study period. Finally, we did not have data on some important predictors for T2D risk, such as the medication in the management of APOs. Future studies may explore the role of these factors in the associations between APOs and future T2D risk.

Conclusions

From a clinical perspective, the knowledge that GDM increases the future risk of T2M is well known and is a key component of the American College of Obstetricians and Gynecologists GDM Practice Bulletin.[85] Furthermore, research and advocacy efforts have increased awareness of the association between HDP and the development of future cardiovascular disease.[86–88] However, there is no widespread knowledge regarding the association of APOs aside from GDM and future risk of diabetes mellitus. This may be due to the strength of the evidence describing APO and future T2D risk. As more longitudinal studies are performed with prospective, validated ascertainment of APOs, there will be more opportunities to study the strength of the association. For example, the Chronic Hypertension and Pregnancy (CHAP) trial included more than 2400 women,[89] and APOs were well characterized. The association between APOs and future T2D risk is being examined in the CHAP Maternal Follow-up Study. In addition, the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) offers excellent prospective ascertainment of APOs as do other studies funded by the Maternal-Fetal Medicine Units Network.[90] We believe that the addition of our data, combined with other observational studies, highlights 2 important points: (1) the need for prospective studies to strengthen the quality of available data and (2) the need for clinical guidelines now while we wait for higher quality data that can potentially enhance screening, improve T2D diagnosis, and reduce T2D complications.

In this large, nationwide cohort of postmenopausal women, a history of GDM, HBW, and HDP increased T2D risk in later life, and those with a history of ≥2 conditions had a greater risk. These APOs are associated with the risk of T2D in the sixth decade of life and beyond and, therefore, should be considered important risk factors while evaluating the risk of developing T2D among postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a Glance

Why was this study conducted?

Beyond gestational diabetes mellitus (GDM), little is known about the associations between other adverse pregnancy outcomes and maternal future risk of type 2 diabetes mellitus.

Key findings

In a nationwide cohort of postmenopausal women, those with a history of GDM, those delivering high-birthweight infants, or those with hypertensive disorders of pregnancy (HDP) were at a higher risk of future diabetes mellitus, and those with a history of ≥2 conditions had higher risks than those with a history of 1 condition.

What does this add to what is known?

Our study provides further evidence for a positive association between HDP and future diabetes mellitus risk. Postmenopausal women with a history of ≥2 adverse pregnancy outcomes are at a higher risk of type 2 diabetes mellitus.

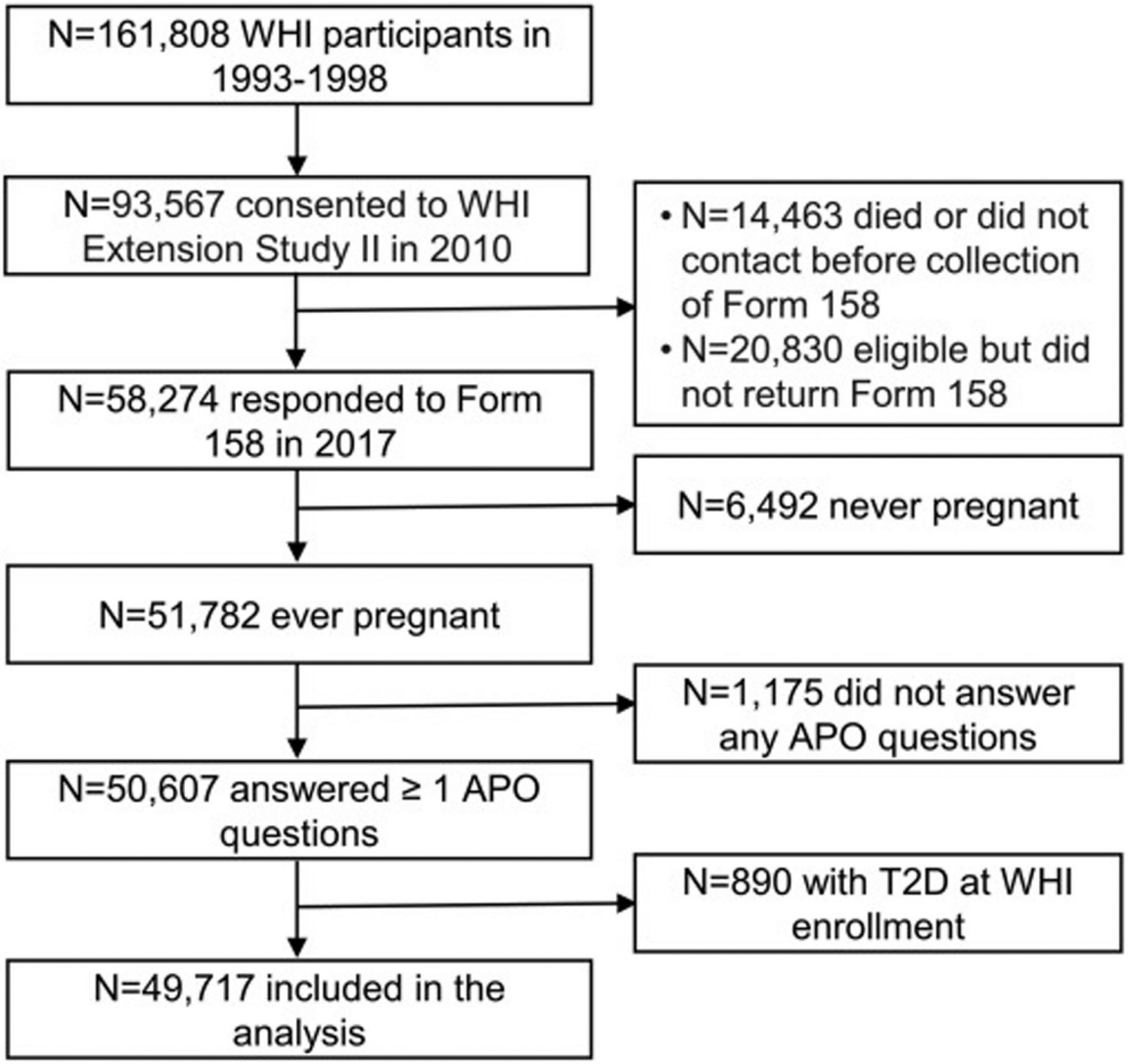

FIGURE 1. Flowchart of the selection of study participants from the WHI study

APO, adverse pregnancy outcome; *T2D*, type 2 diabetes mellitus; *WHI*, Women's Health Initiative.

Zhu. Adverse pregnancy outcomes and future diabetes risk. Am J Obstet Gynecol 2023.

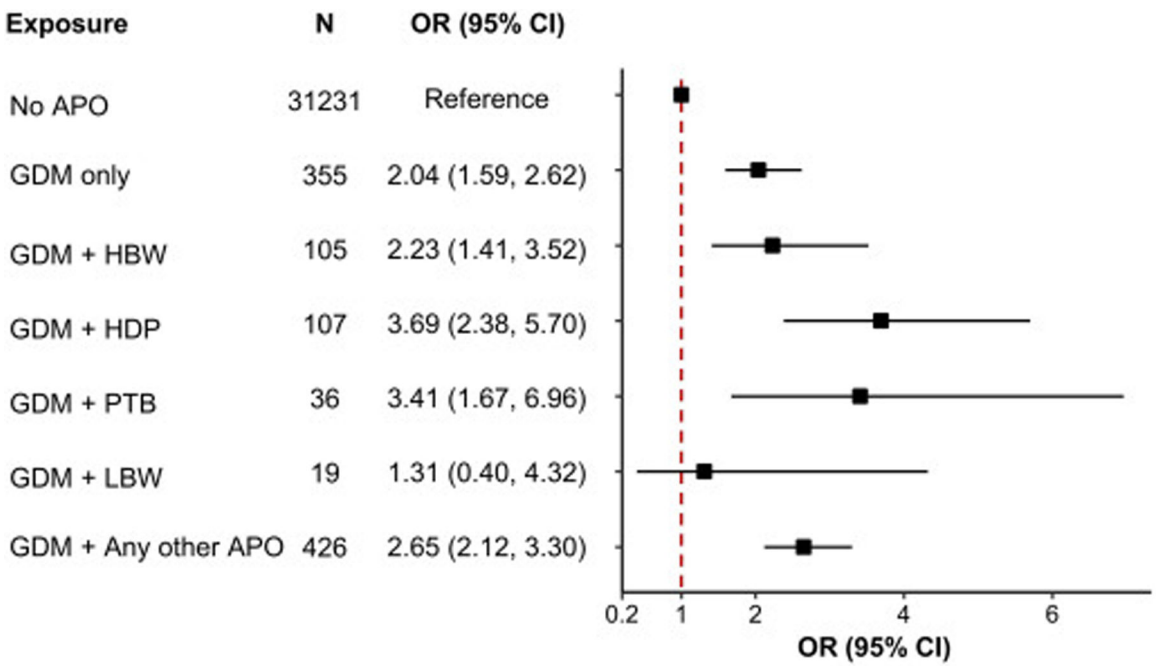

FIGURE 2. Associations between GDM, with or without other APOs, and T2D

"No APO" referred to answering "no" to any APO questions without answering "yes" to other APO questions. All models were adjusted for age at enrollment (continuous), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), education (high school or below, some college, and college and above), annual family income (<$20,000, $20,000–$74,900, and ≥$75,000), body mass index (continuous), physical activity (continuous), age at menarche (≤11, 12–13, and ≥14 years), parity (0–1, 2, 3, 4, and ≥5), age at first birth (never had term pregnancy, <20, 20–29, and ≥30 years), and age at menopause (continuous).

APO, adverse pregnancy outcome; *CI*, confidence interval; *GDM*, gestational diabetes mellitus; *HBW*, high birthweight; *HDP*, hypertensive disorder of pregnancy; *LBW*, low birthweight; *OR*, odds ratio *PTB*, preterm birth.

Zhu. Adverse pregnancy outcomes and future diabetes risk. Am J Obstet Gynecol 2023.

TABLE 1

Baseline characteristics by T2D status and by status of APOs in the Women's Health Initiative (N[49,717)

		T2D status			Any APO[a]			
Characteristics	**Overall**	**No**	**Yes**	***P* value**	**No**	**Yes**	**Uncertain**	***P* value[b]**
Total	49,717 (100)	38,824 (78.1)	10,893 (21.9)		31,231 (62.8)	14,297 (28.8)	4189 (8.4)	
Age at enrollment	60.3 (6.1)	60.3 (6.1)	60.3 (6.1)	.74	60.1 (6.0)	60.2 (5.9)	62.5 (6.4)	.06
Education								
High school or below	8312 (16.8)	6388 (16.6)	1924 (17.8)	<.0001	5002 (16.1)	2492 (17.5)	818 (19.6)	<.0001
Some college	17,944 (36.3)	13,834 (35.9)	4110 (38.0)		10,905 (35.2)	5495 (38.7)	1544 (37.1)	
College and above	23,143 (46.8)	18,356 (47.6)	4787 (44.2)		15,113 (48.7)	6225 (43.8)	1805 (43.3)	
Missing	318	246	72		211	85	22	
Annual family income								
<$20,000	3716 (7.9)	2739 (7.4)	977 (9.4)	<.0001	2124 (7.1)	1127 (8.3)	465 (11.9)	<.0001
$20,000–$74,900	30,550 (64.6)	23,710 (64.2)	6840 (65.8)		18,935 (63.7)	8982 (65.8)	2633 (67.3)	
≥$75,000	13,037 (27.6)	10,460 (28.3)	2577 (24.8)		8676 (29.2)	3545 (26.0)	816 (20.8)	
Missing	2414	1915	499		1496	643	275	
Race and ethnicity								
Non-Hispanic White	44,248 (89.0)	35,017 (90.2)	9231 (84.8)	<.0001	28,062 (89.9)	12,643 (88.5)	3543 (84.7)	<.0001
Non-Hispanic Black	2390 (4.8)	1571 (4.0)	819 (7.5)		1350 (4.3)	750 (5.2)	290 (6.9)	
Hispanic	1429 (2.9)	1034 (2.7)	395 (3.6)		855 (2.7)	436 (3.1)	138 (3.3)	
Other	1627 (3.3)	1186 (3.1)	441 (4.1)		953 (3.1)	461 (3.2)	213 (5.1)	
Missing	23	16	7		11	7	5	
BMI (kg/m^2)	27.2 (5.4)	26.7 (5.1)	29.1 (5.9)	<.0001	26.9 (5.2)	27.8 (5.7)	27.5 (5.5)	<.0001
Physical activity (MET [h/wk])	13.8 (14.0)	14.2 (14.2)	12.2 (13.3)	<.0001	14.1 (14.0)	13.2 (14.0)	13.5 (13.9)	<.0001
AHEI-2010	52.8 (10.4)	53.2 (10.3)	51.6 (10.4)	<.0001	53.1 (10.3)	52.3 (10.4)	52.5 (10.4)	<.0001
Smoking status								
Never smoked	25,876 (52.5)	20,273 (52.7)	5603 (51.9)	<.001	16,451 (53.1)	7261 (51.2)	2164 (52.3)	<.001
Past smoker	21,067 (42.8)	16,470 (42.8)	4597 (42.6)		13,115 (42.4)	6186 (43.6)	1766 (42.7)	
Current smoker	2334 (4.7)	1742 (4.5)	592 (5.5)		1401 (4.5)	727 (5.1)	206 (5.0)	

		T2D status			Any APO[a]			
Characteristics	**Overall**	**No**	**Yes**	***P* value**	**No**	**Yes**	**Uncertain**	***P* value[b]**
Missing	440	339	101		264	123	53	
Alcohol intake								
Nondrinker	3986 (8.1)	3025 (7.8)	961 (8.9)	<.0001	2425 (7.8)	1174 (8.2)	387 (9.3)	<.0001
Past drinker	6855 (13.8)	5092 (13.2)	1763 (16.3)		4036 (13.0)	2168 (15.2)	651 (15.6)	
<7 drinks/wk	32,158 (65.0)	25,151 (65.1)	7007 (64.6)		20,387 (65.6)	9167 (64.4)	2604 (62.5)	
≥7 drinks/wk	6498 (13.1)	5390 (13.9)	1108 (10.2)		4241 (13.6)	1732 (12.2)	525 (12.6)	
Missing	220	166	54		142	56	22	
Age at menarche								
≤11	11,147 (22.5)	8472 (21.9)	2675 (24.6)	<.0001	6724 (21.6)	3489 (24.5)	934 (22.4)	<.0001
12–13	27,784 (56.0)	21,859 (56.4)	5925 (54.6)		17,731 (56.9)	7793 (54.6)	2260 (54.1)	
≥14	10,671 (21.5)	8411 (21.7)	2260 (20.8)		6703 (21.5)	2987 (20.9)	981 (23.5)	
Missing	115	82	33		73	28	14	
Regularity of periods								
No	3902 (7.9)	2933 (7.6)	969 (8.9)	<.0001	2305 (7.4)	1267 (8.9)	330 (7.9)	<.0001
Yes	40,630 (82.1)	31,856 (82.4)	8774 (80.9)		25,765 (82.8)	11,475 (80.6)	3390 (81.4)	
Sometimes regular and sometimes irregular	4982 (10.1)	3886 (10.0)	1096 (10.1)		3036 (9.8)	1503 (10.6)	443 (10.6)	
Missing	203	149	54		125	52	26	
Parity								
0–1	5120 (10.3)	4009 (10.4)	1111 (10.3)	<.0001	3579 (11.5)	1007 (7.1)	534 (12.8)	<.0001
2	15,077 (30.5)	11,946 (30.9)	3131 (28.9)		10,379 (33.4)	3474 (24.4)	1224 (29.4)	
3	14,217 (28.7)	11,162 (28.9)	3055 (28.2)		8955 (28.8)	4088 (28.7)	1174 (28.2)	
4	8280 (16.7)	6424 (16.6)	1856 (17.1)		4820 (15.5)	2794 (19.6)	666 (16.0)	
≥5	6776 (13.7)	5096 (13.2)	1680 (15.5)		3340 (10.7)	2872 (20.2)	564 (13.6)	
Missing	247	187	60		158	62	27	
Age at first birth								
Never had term pregnancy	552 (1.2)	436 (1.2)	116 (1.2)	<.0001	352 (1.2)	102 (0.8)	98 (2.6)	<.0001
<20 y	6269 (13.7)	4727 (13.2)	1542 (15.5)		3471 (12.1)	2272 (17.0)	526 (14.0)	
20–29 y	35,012 (76.5)	27,588 (77.0)	7424 (74.6)		22,234 (77.7)	9990 (74.6)	2788 (74.1)	

		T2D status			Any APO[a]			
Characteristics	**Overall**	**No**	**Yes**	***P* value**	**No**	**Yes**	**Uncertain**	***P* value[b]**
≥30 y	3941 (8.6)	3070 (8.6)	871 (8.8)		2569 (9.0)	1022 (7.6)	350 (9.3)	
Missing	3943	3003	940		2605	911	427	
Breastfeeding ever								
No	20,093 (40.7)	15,543 (40.3)	4550 (42.2)	<.001	12,456 (40.1)	5934 (41.8)	1703 (41.0)	<.01
Yes	29,282 (59.3)	23,045 (59.7)	6237 (57.8)		18,584 (59.9)	8250 (58.2)	2448 (59.0)	
Missing	342	236	106		191	113	38	
Age at menopause	48.6 (5.9)	48.6 (5.8)	48.3 (6.3)	<.0001	48.7 (5.7)	48.1 (6.3)	48.5 (6.2)	<.0001
Family history of diabetes mellitus								
No	33,173 (69.3)	27,010 (72.1)	6163 (59.2)	<.0001	21,291 (70.6)	9218 (67.0)	2664 (67.4)	<.0001
Yes	14,708 (30.7)	10,464 (27.9)	4244 (40.8)		8877 (29.4)	4544 (33.0)	1287 (32.6)	
Missing	1836	1350	486		1063	535	238	

AHEI, Alternative Healthy Eating Index; *APO*, adverse pregnancy outcome; *BMI*, body mass index; *MET*, metabolic equivalent; *T2D*, type 2 diabete mellitus.

[a]Women who answered “no” to all APO questions are included in the “no” column; women who answered “yes” to any APO questions are included in the “yes” column; women who answered “do not know” to any APO questions without answering “yes” to any APO questions are included in the “uncertain” column;

[b]Baseline characteristics were compared between women with and without any APO; women who are included in the “uncertain” group were excluded from these comparisons.

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TABLE 2

Odds ratios and 95% confidence intervals for associations of APOs with T2D in the Women's Health Initiative

Exposure[a]		Total	T2D, n (%)	Model 1[b]	Model 2[c]	Model 3[d]	Model 2 + other APOs	Model 3 + other APOs
Any APO	No	31,231	6298 (20.2)	Ref	Ref	Ref		
	Yes	14,297	3520 (24.6)	1.29 (1.23–1.36)	1.19 (1.13–1.26)	1.17 (1.10–1.24)		
GDM	No	47,287	10,069 (21.3)	Ref	Ref	Ref	Ref	Ref
	Yes	922	372 (40.3)	2.50 (2.19–2.86)	2.26 (1.94–2.63)	2.09 (1.78–2.46)	2.17 (1.83–2.57)	2.01 (1.69–2.40)
HBW	No	46,115	9860 (21.4)	Ref	Ref	Ref	Ref	Ref
	Yes	2836	831 (29.3)	1.52 (1.40–1.66)	1.30 (1.18–1.44)	1.29 (1.16–1.43)	1.22 (1.10–1.36)	1.19 (1.06–1.33)
HDP	No	42,696	8992 (21.1)	Ref	Ref	Ref	Ref	Ref
	Yes	3123	856 (27.4)	1.42 (1.30–1.54)	1.18 (1.08–1.30)	1.18 (1.07–1.30)	1.14 (1.03–1.26)	1.15 (1.03–1.27)
PTB	No	40,912	8824 (21.6)	Ref	Ref	Ref	Ref	Ref
	Yes	7223	1645 (22.8)	1.07 (1.01–1.14)	1.06 (0.99–1.13)	1.05 (0.98–1.13)	1.07 (0.98–1.17)	1.07 (0.98–1.18)
LBW	No	42,623	9294 (21.8)	Ref	Ref	Ref	Ref	Ref
	Yes	6147	1373 (22.3)	1.03 (0.97–1.10)	1.02 (0.95–1.10)	1.00 (0.93–1.08)	0.96 (0.87–1.06)	0.94 (0.85–1.04)
No. of APO								
None		31,231	6298 (20.2)	Ref	Ref	Ref		
1–2		11,570	2695 (23.3)	1.20 (1.14–1.27)	1.13 (1.06–1.20)	1.10 (1.04–1.17)		
>2		651	205 (31.5)	1.82 (1.54–2.15)	1.55 (1.28–1.88)	1.51 (1.24–1.84)		
P value for trend				<.0001	<.0001	0.0001		

APO, adverse pregnancy outcome; *GDM*, gestational diabetes mellitus; *HBW*, high birthweight; *HDP*, hypertensive disorder of pregnancy; *LBW*, low birthweight; *PTB*, preterm birth; *Ref*, reference interval; *T2D*, type 2 diabetes mellitus.

[a]Any APO includes women who answered "yes" to any APO questions; women who answered "no" to any APO questions without answering "yes" to other APO questions were included in the referent group. Women who answered "do not know" or who had missing responses to the specific APO question were excluded from the analysis on the association of that specific APO with T2D;

[b]Crude model;

[c]Adjusted for age at enrollment (continuous), race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), education (high school or below, some college, and college and above), annual family income (<$20,000, $20,000–$74,900, and ≥$75,000), body mass index (continuous), physical activity (continuous), age at menarche (≤11, 12–13, and ≥14 years), parity (0–1, 2, 3, 4, and ≥5), age at first birth (never had term pregnancy, <20, 20–29, ≥30 years), and age at menopause (continuous);

[d]Model 2 + region at enrollment (Northeast, South, Midwest, and West), study component (observational studies and clinical trials), randomization arm (hormone therapy, dietary modification, and calcium or vitamin D supplementation), Alternative Healthy Eating Index-2010 (continuous), smoking (never, past, and current), pack-years of smoking (never, 5, 5–19, and ≥20 cigarettes/day), alcohol intake

(never, past, <7 drinks/wk, and ≥7 drinks/wk), regularity of periods (no, yes, and sometimes regular and sometimes irregular), breastfeeding ever (no or yes), and family history of diabetes mellitus (no or yes).

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TABLE 3

Associations of APOs with T2D among subgroups[a]

Variable	Any APO[b]	GDM[b,c]	HBW[b,c]	HDP[b,c]	PTB[b,c]	LBW[b,c]
BMI at enrollment (kg/m^2)						
<25.0	1.13 (1.02–1.25)	1.95 (1.39–2.72)[d]	0.96 (0.74–1.24)	1.04 (0.83–1.30)	1.09 (0.93–1.28)	0.90 (0.75–1.07)
25.0–29.9	1.20 (1.09–1.31)[d]	1.96 (1.47–2.60)[d]	1.40 (1.18–1.66)[d]	1.30 (1.10–1.54)	0.99 (0.85–1.15)	1.01 (0.86–1.19)
≥30.0	1.24 (1.13–1.37)[d]	2.43 (1.84–3.22)[d]	1.21 (1.02–1.44)	1.04 (0.89–1.22)	1.17 (1.00–1.36)	0.98 (0.82–1.16)
P value for interaction	.309	.294	.087	.098	.223	.440
Race and ethnicity						
Non-Hispanic White	1.19 (1.12–1.26)[d]	2.14 (1.78–2.57)	1.24 (1.11–1.39)[d]	1.14 (1.02–1.27)	1.07 (0.97–1.17)	0.94 (0.85–1.04)
Non-Hispanic Black	1.53 (1.21–1.93)[d]	0.94 (0.40–2.23)	2.03 (1.11–3.72)	1.14 (0.78–1.66)	1.35 (0.91–2.01)	1.44 (0.98–2.12)
Hispanic	0.93 (0.66–1.30)	2.97 (1.20–7.33)	0.68 (0.33–1.40)	1.21 (0.68–2.13)	0.56 (0.31–1.01)	0.92 (0.50–1.70)
Other	1.18 (0.89–1.57)	3.13 (1.60–6.13)	0.73 (0.31–1.71)	1.21 (0.69–2.10)	1.39 (0.89–2.16)	0.75 (0.46–1.22)
P value for interaction	.036	.729	.434	.945	.160	.065
Education						
High school and below	1.11 (0.97–1.27)	1.94 (1.23–3.04)	1.31 (1.03–1.68)	1.03 (0.81–1.31)	0.90 (0.71–1.14)	1.11 (0.87–1.41)
College and above	1.21 (1.14–1.28)[d]	2.21 (1.85–2.65)[d]	1.20 (1.06–1.36)	1.16 (1.04–1.3)	1.10 (1.00–1.21)	0.94 (0.85–1.04)
P value for interaction	.341	.606	.536	.541	.184	.889
Parity						
0–2	1.16 (1.06–1.27)	1.52 (1.11–2.08)	1.16 (0.91–1.48)	1.17 (0.99–1.38)	1.07 (0.92–1.25)	0.95 (0.80–1.13)
>2	1.21 (1.13–1.30)[d]	2.54 (2.08–3.12)[d]	1.24 (1.09–1.40)[d]	1.12 (0.99–1.27)	1.07 (0.96–1.19)	0.97 (0.86–1.09)
P value for interaction	.436	.006	.587	.966	.957	.851
Breastfeeding ever						
No	1.19 (1.09–1.30)[d]	2.03 (1.51–2.72)[d]	1.36 (1.13–1.63)	1.13 (0.96–1.32)	1.06 (0.92–1.21)	1.02 (0.89–1.18)
Yes	1.18 (1.10–1.27)[d]	2.24 (1.82–2.76)[d]	1.15 (1.01–1.32)	1.14 (1.00–1.30)	1.09 (0.97–1.23)	0.89 (0.78–1.02)
P value for interaction	.997	.761	.248	.984	.750	.265
Age at first birth (y)						
<30	1.17 (1.11–1.24)[d]	2.16 (1.81–2.58)[d]	1.22 (1.09–1.37)[d]	1.12 (1.00–1.24)	1.05 (0.96–1.15)	0.98 (0.88–1.08)

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Variable	Any APO[b]	GDM[b,c]	HBW[b,c]	HDP[b,c]	PTB[b,c]	LBW[b,c]
≥30	1.46 (1.21–1.76)[d]	2.08 (1.17–3.7)	1.16 (0.75–1.79)	1.44 (1.03–2.01)	1.43 (1.05–1.95)	0.81 (0.56–1.16)
P value for interaction	.051	.936	.702	.251	.099	.966

P values for interaction before multiple comparison were shown in the table. None were statistically significant after Benjamini-Hochberg correction.

APO, adverse pregnancy outcome; *BMI*, body mass index; *GDM*, gestational diabetes mellitus; *HBW*, high birthweight; *HDP*, hypertensive disorder of pregnancy; *LBW*, low birthweight; *PTB*, preterm birth; *T2D*, type 2 diabetes mellitus.

[a]Any APO includes women who answered “yes” to any APO questions; women who answered “no” to any APO questions without answering “yes” to other APO questions were included in the referent group. Women who answered “do not know” or who had missing responses to the specific APO question were excluded from the analysis on the association of that specific APO with T2D;

[b]Models adjusted for age at enrollment (continuous), race and ethnicity (non-Hispanic White, Non-Hispanic Black, Hispanic, and other), education (high school or below, some college, and college and above), annual family income (<$20,000, $20,000–$74,9000, and ≥$75,000), BMI (continuous), physical activity (continuous), age at menarche (≤11, 12–13, and ≥14 years), parity (0–1, 2, 3, 4, and ≥5), age at first birth (never had term pregnancy, <20, 20–29, and ≥30 years), and age at menopause (continuous);

[c]Models additionally adjusted for other APOs;

[d]Indicates statistical significance accounting for multiple comparison using Benjamini-Hochberg correction.

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