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Clinical Research Article

Maternal Diabetes in Youth-Onset Type 2 Diabetes Is Associated With Progressive Dysglycemia and Risk of Complications

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Abstract

Context: Prenatal exposures, including undernutrition, overnutrition, and parental diabetes, are recognized risk factors for future cardiometabolic disease. There are currently no data on effects of parental diabetes on disease progression or complications in youth-onset type 2 diabetes (T2D).

Objective: We analyzed effects of parental diabetes history on glycemic outcomes, β-cell function, and complications in a US cohort of youth-onset T2D.

Methods: Participants (N = 699) aged 10 to 17 years with T2D were enrolled at 15 US centers and followed for up to 12 years as part of the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) and TODAY2 follow-up studies. Information about diabetes diagnosis in biological mothers was available for 621 participants (never = 301; before or during pregnancy = 218; after pregnancy = 102) and in biological fathers for 519 (no diabetes = 352; paternal diabetes = 167).

Results: Maternal, but not paternal, diabetes was associated with loss of glycemic control over time, defined as glycated hemoglobin A_{1c} greater than or equal to 8% for more than 6 months ($P = .001$). Similarly, maternal, but not paternal, diabetes was associated with increased risk of glomerular hyperfiltration ($P = .01$) and low heart rate variability ($P = .006$) after 12 years of follow-up. Effects were largely independent of age, sex, race/ethnicity, and household income. Maternal diabetes during vs after pregnancy had similar effects on outcomes.

Conclusion: Maternal diabetes, regardless of whether diagnosed during vs after pregnancy, is associated with worse glycemic control, glomerular hyperfiltration, and reduced heart rate variability in youth with T2D in TODAY. The strong associations of diabetes outcomes with maternal diabetes suggest a possible role for in utero programming.

Key Words: maternal diabetes, dysglycemia, hyperfiltration, heart rate variability, type 2 diabetes, youth

Abbreviations: $\Delta C_{30}/\Delta G_{30}$, increment of C-peptide over increment of glucose during first 30 minutes of 75-g oral glucose tolerance test; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; NPDR, nonproliferative diabetic retinopathy; oDI, oral disposition index; OGTT, oral glucose tolerance test; SDNN, SD of normal R-R interval; T2D, type 2 diabetes; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth; UACR, urine albumin-creatinine ratio.

Prenatal nutritional and environmental exposures are recognized risk factors for chronic diseases in later life, including obesity and type 2 diabetes (T2D) (1). Studies in animal models and human populations show that exposure to maternal diabetes and features of the diabetic environment—including maternal obesity, insulin resistance, and hyperglycemia—during critical windows in development can induce epigenetic and metabolic adaptations that increase chronic disease risk for offspring (2). Thus, optimizing mothers' metabolic health before and during pregnancy is emphasized to promote child health (3). Although paternal effects are less widely studied, recent data implicate fathers'

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weight and diabetes status as contributors to chronic disease risk in progeny (4, 5).

Although parental diabetes is linked to β-cell dysfunction and accelerated onset of T2D in offspring (6-8), less is known about whether parental diabetes affects disease progression and/or complications in youth-onset T2D. Youth with T2D are more insulin resistant and have a more rapid decline of β-cell function than adults with T2D (9), are less likely to respond to standard therapies (10), and have accelerated onset of complications (11). With rising rates of youth-onset T2D (12), identifying predictors and mediators of the more aggressive clinical course in youth is an important research priority.

Much of what is currently known about T2D in youth has emerged from the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, a National Institutes of Health–funded multicenter study designed to identify treatments for, and understand the natural history of, pediatric-onset T2D (10). Prior analyses in TODAY showed that diabetes diagnosis in either parent was associated with younger age at diagnosis, higher glycated hemoglobin A_{1c} (HbA_{1c}), impaired β-cell function, and loss of glycemic control in the first 4 years of the study (13, 14). However, evidence is limited regarding longer-term effects of parental diabetes on disease progression and rate of complications in youth-onset T2D. Thus, we conducted a secondary analysis in the TODAY cohort to test whether parental diabetes diagnosis alters the clinical course over 12 years of study follow-up. Our primary aims were to examine effects of diabetes diagnosis in either parent on glycemic control, β-cell function, and risk of microvascular and macrovascular complications. To explore potential effects of hyperglycemia in utero, a secondary analysis examined whether maternal diabetes diagnosed before or during pregnancy, compared to after pregnancy, has a differential effect on the described outcomes.

Materials and Methods

Study Design

Detailed descriptions of the TODAY protocol (https://clinicaltrials.gov/ct2/show/NCT00081328: NCT0008132) and primary outcome results have been published previously (10, 11, 15). In brief, 699 participants with T2D diagnosed at age younger than 18 years, with diabetes for less than 2 years, body mass index (BMI) greater than the 85th percentile for age and sex, negative islet-cell antibodies, and C-peptide greater than 0.6 ng/mL were randomly assigned at 15 sites to receive metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention. The primary goal of TODAY (2004-2011) was to evaluate effects of these treatments on loss of glycemic control ($HbA_{1c} \geq 8\%$ for > 6 months or failure to wean insulin after acute decompensation). Study visits occurred every 2 months for 1 year and quarterly thereafter.

In 2011, 572 (82%) TODAY participants enrolled in the TODAY2 post-intervention follow-up study. Between 2011 and 2014, participants no longer received randomized treatment, but continued to receive diabetes-related care through the study with quarterly visits. From 2014 to 2020, 518 (74% of original cohort) participants remained enrolled, transitioned to community care, and had annual observational visits. Participants were followed for an average of 10.2 ± 4.5 years. TODAY and TODAY2 were approved by the institutional review board at all centers and all participants and guardians provided written informed assent and/or consent.

Study Evaluations and Assessments

Baseline demographic factors were collected as described previously (11, 16, 17). Participant birth weight, parental age at participants' birth, history of diabetes in biological parents (including age of diagnosis), and current maternal BMI were obtained through interview with a parent/caregiver. We classified parental history of diabetes into 4 categories: neither parent (neither), both parents (both), mother only (mother), and father only (father). We further classified maternal history of diabetes into 3 categories to evaluate whether the timing of the maternal diabetes diagnosis (in utero exposure to hyperglycemia) might affect outcomes: diagnosed before or during pregnancy (during), diagnosed after pregnancy (after), or never diagnosed (never). Paternal history of diabetes was classified into "never" vs "ever" categories regardless of timing.

Detailed study procedures in TODAY and TODAY2 have been described previously (16). Each study visit included medical history and examination. HbA_{1c} and fasting laboratory tests were obtained according to standardized procedures and analyzed by the TODAY Central Biochemistry Laboratory (CBL; insulin RRID:AB_2924338; C-peptide RRID:AB_2924337). Oral glucose tolerance tests (OGTTs) were collected at baseline, months 6 and 24, and annually during TODAY through 2014, and at 6 and 9 years in TODAY2. Surrogate markers of insulin sensitivity (1/fasting insulin, 1/fasting C-peptide) and β-cell function (C-peptide index [ratio of change in C-peptide over change in glucose between 0 and 30 minutes during OGTT] and the C-peptide oral disposition index [oDI 1: product of insulin sensitivity × C-peptide index; and oDI 2: the product of C-peptide inverse × C-peptide index, 2 measures of β-cell function relative to markers of insulin sensitivity]), were calculated (17). Estimated glomerular filtration rate (eGFR) was calculated using the Full Age Spectrum equation and hyperfiltration defined as eGFR greater than or equal to 135 mL/min/1.73 m^2 at 2 or more consecutive visits. Fundus photography was performed twice (2010-2011 and 2017-2018), as were measures of cardiovascular function (arterial stiffness and heart rate variability) (2013-2014 and 2018-2019) and processed at a centralized reading center (11). Definitions for longitudinal assessments of hypertension, dyslipidemia, microalbuminuria, and neuropathy have been previously described (10, 11, 15).

Statistical Analyses

Baseline characteristics by parental diabetes group were compared using the Wilcoxon rank sum test for quantitative variables and chi-square test for categorical variables. Variables with a skewed distribution were log-transformed before testing as indicated. The Kaplan-Meier method was used to estimate cumulative incidence of time-to-event outcomes (eg, loss of glycemic control and hyperfiltration), and the log-rank test was used to compare incidence curves by groups. As the number at risk beyond year 12 declined as a function of staggered entry into the cohort, results were presented up to year 12. Cox proportional hazards models were used to estimate incident risk of time-to-event outcomes after adjustment for participant demographic and socioeconomic factors (age, sex, race-ethnicity, and household income). Randomization

assignment was evaluated, but not retained, in the analyses due to lack of effect. Similarly, parental age was considered as a potential confounder but was not retained, as parental age varied across the various parental and maternal diabetes groups but was not univariately associated with any of the outcomes. Participants with the event at baseline were excluded from time-to-event analyses. Multivariable linear mixed regression models, adjusted for similar covariates, were used to evaluate the effects of parental diabetes group on the mean of continuous outcomes (eg, HbA_{1c} and β-cell function indices) over repeated time points. Similar linear or logistic regression multivariable models were used to evaluate the association between parental diabetes group with retinopathy and cardiovascular outcomes (evaluated at the time of follow-up assessment in the study as well as the follow-up minus initial assessment change in measures). Interaction terms of participant sex with parental diabetes group were added in separate models to evaluate if associations differed by sex. All analyses were considered exploratory and statistical significance was defined as P less than .05.

Results

Of 699 TODAY participants, 22 were subsequently found to have monogenic diabetes mutations and excluded. Information on parental diabetes diagnosis was obtained for 621 mothers and 519 fathers, with combined parental history available for 486 participants. Among participants with complete data (n = 486), maternal diabetes (52.7%) was reported more commonly than paternal diabetes (31.1%). Combining parents' histories, 79 (16.3%) participants reported diabetes in both parents (both), 177 (36.4%) reported only maternal diabetes (mother), 72 (14.8%) reported only paternal diabetes (father), and 158 (32.5%) reported no parental diabetes (neither). Of the 621 participants with complete maternal diabetes history data, 218 (35.1%) reported maternal diabetes diagnosed before or during pregnancy (during), 102 (16.4%) reported maternal diabetes diagnosed after pregnancy (after), and 301 (48.5%) reported no maternal diabetes (never).

Baseline demographic and clinical characteristics according to maternal and parental history of diabetes have been published in similar samples (not excluding participants with monogenic diabetes mutations) (13). These data, along with additional characteristics of interest (household income and education, eGFR, urine albumin-creatinine ratio [UACR], and lipids), are shown in Table 1. As previously reported, nominally significant baseline factors at the .1 level found to be associated with diagnosis of maternal diabetes during pregnancy (vs after pregnancy or never) included younger participant age at diabetes diagnosis, higher birth weight, older parental age, higher HbA_{1c}, and lower β-cell function (C-peptide index and oDI) (13). Significant baseline factors found to be associated with diagnosis of paternal diabetes (vs never) included female sex, older parental age, and higher HbA_{1c} (13). Race/ethnicity, maternal BMI at randomization, and participant anthropometrics (BMI, percentage of fat from dual-energy x-ray absorptiometry, and waist circumference) were similar across groups (13). Parental diabetes diagnosis ("both" group) was associated with lower household income ($P = .04$). No difference in household education, blood pressure, eGFR, UACR, or lipids was identified across the 4 parental diabetes or the 3 maternal diabetes groups (see Table 1).

Effects of Parental Diabetes Diagnosis

Longitudinal measures of glycemic control and glucose metabolism

Parental diabetes diagnosis was significantly associated with glycemic control over time. Fig. 1A shows the cumulative incidence of loss of glycemic control (defined as sustained $HbA_{1c} \geq 8\%$) over 12 years of follow-up. Participants in the mother or both groups were more likely to lose glycemic control, compared with the neither group (cumulative incidence, both: 90.4%; mother: 85.5%; neither: 70.4%; both vs neither; $P = .003$, mother vs neither; $P = .03$). Although cumulative incidence of loss of glycemic control in the father group was similar to the both and mother groups within the first 4 years after randomization, the father group subsequently became more similar to the neither group (12-year cumulative incidence: father (69.2%); neither (70.4%); $P = .24$). Effects of maternal and biparental diabetes on loss of glycemic control remained statistically significant after adjustment for demographic and socioeconomic factors (age, sex, race-ethnicity, and household income). Per study protocol, none of the participants were under insulin therapy at study baseline. Prescribed insulin medication increased over time, with year 12 frequencies as follows: both (59.2%), mother (61.6%), father (57.9%), and neither (43.0%); $P = .06$ for overall difference).

Table 2 shows the effect of parental diabetes on longitudinal differences in glycemia (assessed by HbA_{1c}) and markers of insulin sensitivity and β-cell function, before and after adjustment for sociodemographic covariates. Participants in the both and mother groups had significantly higher HbA_{1c} levels (Fig. 2A; $P = .008$) and lower C-peptide index and C-peptide–based oDI levels (Fig. 2B and 2C; $P = .004$ and $P = .002$, respectively) over time, compared to the neither group, in unadjusted models. Differences in C-peptide index across groups remained significant after adjustment for sociodemographic confounders, whereas differences in HbA_{1c} and C-peptide oDI were attenuated and no longer significant ($P = .06$ and $P = .07$, respectively). By contrast, longitudinal measures of insulin sensitivity, 1/fasting C-peptide, and insulin-based oral disposition index did not differ according to parental diabetes diagnosis groups.

Diabetes Complications and Comorbidities

Parental diabetes diagnosis was associated with a higher incidence of glomerular hyperfiltration (Fig. 1B) in unadjusted models. Participants in the mother and both groups had a higher cumulative incidence of glomerular hyperfiltration than the neither and father groups (both: 60.2%; mother: 55.2%; father: 37.3%; neither: 38.6%; both vs neither; $P = .03$; mother vs neither; $P = .03$). Incidence in the father group was not significantly different from the both or mother groups, likely because of the small number of participants in the father group at later time points. The differences remained significant after adjustment for cumulative glycemia defined as the time-weighted mean HbA_{1c} (data not shown); however, differences among the groups were attenuated after adjustment for sociodemographic covariates (adjusted $P = .13$). No significant interaction by participant sex was found in either model (data not shown). No other associations over time were found for any other outcomes (hypertension,

Table 1. Demographic and baseline metabolic characteristics of Treatment Options for type 2 Diabetes in Adolescents and Youth participants by parental and maternal history of diabetes

Characteristics	Parental history of diabetes (n = 486)					Maternal history of diabetes (n = 621)			
	Both parents (n = 79)	Mother only (n = 177)	Father only (n = 72)	Neither parent (n = 158)	*P*	During or before pregnancy (n = 218)	After pregnancy (n = 102)	Never diagnosed (n = 301)	*P*
Demographic									
Age, y[b]	13.6 ± 2.0	13.9 ± 2.1	14.2 ± 2.1	14.0 ± 1.9	.27	13.6 ± 2.1	14.2 ± 1.9	14.2 ± 2.0	.001
Female, %[b]	73.4	59.9	70.8	63.3	.12	60.6	71.6	68.1	.09
Race/ethnicity, %[b]									
Black non-Hispanic	29.1	29.9	31.9	33.5	.68	32.1	30.4	34.2	.81
Hispanic	43.0	40.1	38.9	37.3		40.8	43.1	37.9	
White non-Hispanic	15.2	22.6	25.0	21.5		19.3	18.6	21.9	
Other	12.7	7.3	4.2	7.6		7.8	7.8	6.0	
Household income, %									
< $25 000	52.8	37.8	30.4	31.3	.04	50.0	41.9	36.1	.04
$25 000-$49 999	23.6	34.0	30.4	36.8		29.1	34.4	35.0	
≥ $50 000	23.6	28.2	39.1	31.9		20.9	23.7	28.9	
Household education, %									
< High school	31.7	26.0	22.2	17.1	.10	28.9	31.4	22.9	.13
High school/GED	24.1	27.1	27.8	20.9		24.3	30.4	25.3	
College no degree	29.1	32.8	33.3	36.7		32.6	29.4	32.6	
Graduate degree	15.2	14.1	16.7	25.3		14.2	8.8	19.3	
Perinatal[b]									
Birth weight, g	3506 ± 773	3461 ± 925	3034 ± 717	3223 ± 676	< .0001	3503 ± 928	3335 ± 746	3177 ± 701	< .0001
Maternal age, y	29.5 ± 6.4	27.7 ± 5.9	26.2 ± 5.4	25.7 ± 5.5	< .0001	28.9 ± 6.2	26.4 ± 5.8	25.8 ± 5.6	< .0001
Paternal age, y	33.6 ± 9.2	30.0 ± 6.2	29.6 ± 6.3	28.0 ± 6.6	< .0001	31.6 ± 7.5	29.5 ± 6.9	28.6 ± 6.5	< .0001
Maternal BMI	36.4 ± 9.6	34.2 ± 9.6	34.1 ± 9.3	33.2 ± 8.1	.12	34.5 ± 9.5	36.0 ± 9.7	33.9 ± 8.7	.15
Anthropometric[b]									
BMI	35.6 ± 8.3	34.6 ± 6.8	35.6 ± 9.0	34.9 ± 7.3	.93	35.2 ± 8.2	34.5 ± 6.5	35.3 ± 7.7	.85
BMI *Z* score	2.3 ± 0.5	2.3 ± 0.4	2.2 ± 0.4	2.2 ± 0.5	.87	2.3 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	.21
% body fat from DXA	38.2 ± 6.3	38 ± 6.8	37.7 ± 6.1	37.3 ± 5.8	.73	37.9 ± 6.5	38.2 ± 6.2	37.6 ± 5.9	.64
Blood pressure									
Systolic, mm Hg	113.1 ± 10.3	114.1 ± 11.7	113.3 ± 10.5	111.9 ± 11	.32	114.3 ± 11.3	112.7 ± 10.5	112.6 ± 10.7	.24
Diastolic, mm Hg	66.8 ± 8.8	66.8 ± 8.7	66.3 ± 6.9	66.1 ± 8.4	.79	67.3 ± 8.7	66.3 ± 8.1	66.3 ± 7.9	.41
Metabolic									
HbA_{1c}, %[b]	6.2 ± 0.8	6.1 ± 0.8	6.0 ± 0.7	5.8 ± 0.6	< .0001	6.2 ± 0.8	6.1 ± 0.7	5.9 ± 0.7	< .0001
Insulin sensitivity, $1/I_F$, mL/μU[b]	0.06 ± 0.07	0.05 ± 0.04	0.05 ± 0.05	0.05 ± 0.04	.79	0.05 ± 0.05	0.06 ± 0.06	0.05 ± 0.04	.16
C-peptide inverse, $1/I_C$, mL/ng	0.31 ± 0.13	0.31 ± 0.13	0.29 ± 0.12	0.32 ± 0.17	.89	0.31 ± 0.14	0.31 ± 0.13	0.30 ± 0.15	.27

(*continued*)

Table 1. Continued

Characteristics	Parental history of diabetes (n = 486)					Maternal history of diabetes (n = 621)			
	Both parents (n = 79)	Mother only (n = 177)	Father only (n = 72)	Neither parent (n = 158)	*P*	During or before pregnancy (n = 218)	After pregnancy (n = 102)	Never diagnosed (n = 301)	*P*
C-peptide index, $\Delta C_{30}/\Delta G_{30}$, ng/mL per mg/dL[b]	0.063 ± 0.052	0.066 ± 0.061	0.079 ± 0.069	0.115 ± 0.210	< .0001	0.064 ± 0.059	0.063 ± 0.049	0.102 ± 0.160	< .0001
oDI 1, $1/I_F \times \Delta C_{30}/\Delta G_{30}$[b]	0.003 ± 0.005	0.003 ± 0.004	0.003 ± 0.003	0.005 ± 0.011	.003	0.003 ± 0.004	0.003 ± 0.004	0.004 ± 0.010	.004
oDI 2, $1/C_F \times \Delta C_{30}/\Delta G_{30}$	0.018 ± 0.013	0.019 ± 0.016	0.022 ± 0.020	0.033 ± 0.059	< .0001	0.018 ± 0.015	0.018 ± 0.014	0.028 ± 0.045	< .0001
eGFR, mL/min/1.73 m²	119.4 ± 15.8	121.7 ± 15.0	119.8 ± 15.0	118.6 ± 16.9	.33	120.7 ± 15.7	121.8 ± 16.0	119.1 ± 16.8	0.27
UACR, mg/g	39.6 ± 155.0	21.7 ± 76.0	38.5 ± 93.0	34.7 ± 113.1	.40	25.5 ± 102.7	40.2 ± 176.8	32.2 ± 96.8	.61
Total cholesterol, mg/dL	145 ± 29.5	147.7 ± 26.6	146.1 ± 26.9	146.2 ± 31.6	.63	148.9 ± 27.2	143.6 ± 27.9	145.7 ± 30.6	.27
LDL-C, mg/dL	83.5 ± 23.5	86.9 ± 22.5	83.3 ± 22.9	84.3 ± 26	.43	87.4 ± 23.2	83.9 ± 22.4	83.9 ± 25.8	.24
HDL-C, mg/dL	38.7 ± 8.3	38.6 ± 8.4	38.9 ± 8.9	38.3 ± 8.6	.98	39.4 ± 8	38.1 ± 9.3	38.3 ± 8.8	.11
Triglycerides, mg/dL	116.2 ± 65.5	115.5 ± 81.2	121 ± 91.1	120.1 ± 88.3	.74	110.4 ± 65.1	117.7 ± 87.1	119.1 ± 84.6	.48

Baseline refers to time of TODAY randomization[a].
Perinatal factors (birth weight, maternal and paternal age) were assessed at participant's birth except for maternal BMI (self-reported) that was available only at study baseline. Baseline characteristics were compared by parental or maternal history of diabetes status using the Wilcoxon rank sum test for quantitative variables and chi-square tests for categorical variables.
Abbreviations: $\Delta C_{30}/\Delta G_{30}$, increment of C-peptide over increment of glucose during first 30 minutes of 75-g oral glucose tolerance test; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; GED, graduate equivalency degree; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; oDI, oral disposition index; TODAY, Treatment Options for type 2 Diabetes in Adolescents and Youth; UACR, urine albumin-creatinine ratio.
[a]Mean ± SD or percentage are shown.
[b]Results have been previously published in similar samples (13).

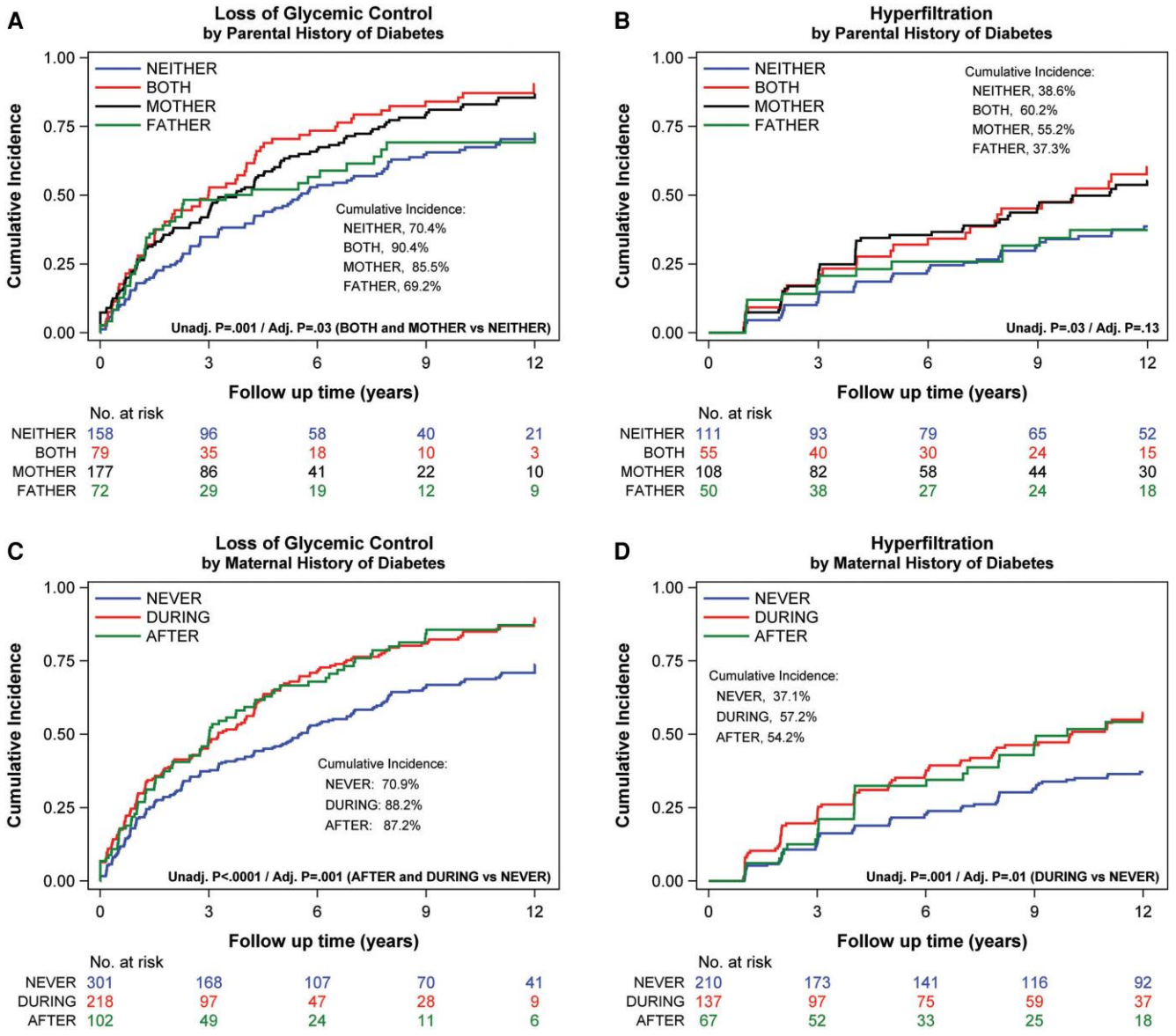

Figure 1. Cumulative incidence of loss of glycemic control and hyperfiltration by A and B, parental and C and D, maternal history of diabetes over 12 years of follow-up. Kaplan-Meier cumulative incidence probability curves for loss of glycemic control (sustained glycated hemoglobin $A_{1c} \geq 8\%$) and hyperfiltration (sustained estimated glomerular filtration rate ≥ 135 mL/min/1.73 m²), with number of participants at risk at 0, 3, 6, 9 and 12 years. The number at risk beyond year 12 declines as a function of staggered entry into the cohort (2004-2008); therefore, results are presented up to year 12 in the study. Cumulative incidence rates at year 12 and *P* values from unadjusted (Unadj.) models (log-rank *P*) and adjusted (Adj.) models (from Cox proportional hazards models adjusted for participant age, sex, race-ethnicity, and highest level of household annual income at baseline are shown within each figure panel.

dyslipidemia, microalbuminuria, and neuropathy) in relation to parental diabetes groups.

Table 3 shows cross-sectional associations between parental diabetes groups with markers of retinopathy and cardiovascular measures. Although we did not observe any differences in prevalence of retinopathy or in measures of arterial stiffness, maternal diabetes diagnosis was associated with heart rate variability, a surrogate measure for autonomic neuropathy. The SD of the normal R-R interval (SDNN) was lower in the mother group, compared with the neither group ($P = .003$). Similarly, the 5-year change in SDNN was greater in the mother group compared with the neither group ($P = .002$). These differences remained significant after adjustment for sociodemographic confounders.

Effects of Maternal Diabetes During vs After Pregnancy

Longitudinal measures of glycemic control and glucose metabolism

We observed a statistically significant association between maternal diabetes diagnosis and glycemic control over time. Cumulative incidence of loss of glycemic control (defined as sustained $HbA_{1c} \geq 8\%$) over 12 years of follow-up was higher in participants with a maternal diabetes diagnosis, regardless of the timing of the diagnosis. Cumulative incidence of loss of glycemic control was 88.2% for participants in the during group, 87.2% in the after group, and 70.9% in the never group (Fig. 1C; during vs never; $P = .0004$ and after vs never;

Table 2. Model-derived longitudinal means of glycated hemoglobin A_{1c}, markers of insulin sensitivity and β-cell function, and estimated glomerular filtration rate, by parental and maternal history of diabetes group over 12 years of follow-up[a]

	Parental history of diabetes (n = 486)						Maternal history of diabetes (n = 621)				
Outcome	Both parents (n = 79)	Mother only (n = 177)	Father only (n = 72)	Neither parent (n = 158)	Unadj. *P*	Adj. *P*	During or before pregnancy (n = 218)	After pregnancy (n = 102)	Never diagnosed (n = 301)	Unadj. *P*	Adj. *P*
HbA_{1c}, %	7.9 ± 0.2	7.8 ± 0.1	7.7 ± 0.2	7.2 ± 0.1	.008	.06	8.0 ± 0.1	7.8 ± 0.2	7.4 ± 0.1	.0004	.01
Insulin sensitivity, $1/I_F$, mL/μU[b]	0.04 ± 0.82	0.04 ± 0.88	0.03 ± 0.80	0.03 ± 0.87	.25	.06	0.04 ± 0.89	0.04 ± 0.84	0.03 ± 0.90	.07	.01
C-peptide inverse, $1/I_C$, mL/ng[b]	0.37 ± 0.94	0.36 ± 0.96	0.36 ± 0.94	0.34 ± 0.96	.61	.29	0.37 ± 0.96	0.36 ± 0.95	0.34 ± 0.97	.12	.13
C-peptide index, $\Delta C_{30}/\Delta G_{30}$, ng/mL per mg/dL[b]	0.024 ± 0.673	0.026 ± 0.767	0.030 ± 0.669	0.037 ± 0.778	.004	.06	0.025 ± 0.785	0.024 ± 0.702	0.035 ± 0.831	.0002	.007
oDI 1, $1/I_F \times \Delta C_{30}/\Delta G_{30}$[b]	0.001 ± 0.434	0.001 ± 0.567	0.001 ± 0.410	0.001 ± 0.566	.06	.28	0.001 ± 0.597	0.001 ± 0.470	0.002 ± 0.655	.03	.39
oDI 2, $1/C_F \times \Delta C_{30}/\Delta G_{30}$[b]	0.009 ± 0.660	0.009 ± 0.753	0.011 ± 0.649	0.013 ± 0.759	.002	.07	0.009 ± 0.774	0.009 ± 0.686	0.012 ± 0.814	.0002	.006
eGFR, mL/min/1.73 m²	129.0 ± 2.3	131.6 ± 1.6	127.5 ± 2.6	126.2 ± 1.7	.13	.27	130.0 ± 1.5	132.1 ± 2.1	126.8 ± 1.2	.05	.25

P values shown for unadjusted (Unadj. *P*) and models adjusted (Adj. *P*) for participant age, sex, race-ethnicity, and highest level of household annual income at baseline.
Abbreviations: $\Delta C_{30}/\Delta G_{30}$, increment of C-peptide over increment of glucose during first 30 minutes of 75-g oral glucose tolerance test; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; oDI, oral disposition index.
[a]Model-derived mean (or geometric mean for log-transformed outcomes) estimates ± SE obtained from linear mixed models over 12 years of follow-up are shown.
[b]Values log-transformed before testing to approximate normality.

P = .01). At year 12, prescribed insulin medication was highest in the during (62.3%), intermediate in the after (55.4%), and lowest in the never (44.8%) group (*P* = .01 for overall difference).

Table 2 shows the effect of maternal diabetes on longitudinal measures of glycemia and insulin homeostasis, before and after adjustment for covariates. Over the 12 years of follow-up, participants in the during and after groups had significantly higher HbA_{1c} (Fig. 2D; *P* = .0004), and lower C-peptide index and oDI; (Fig. 2E and 2F; *P* = .0002 and *P* = .002, respectively), compared to the never group. After adjustment for sociodemographic factors, differences in HbA_{1c}, C-peptide index, and C-peptide–based oDI remained significant across maternal diabetes diagnosis categories. No differences between the during and after groups were identified.

Diabetes Complications and Comorbidities

Maternal diabetes diagnosis was associated with higher 12-year cumulative incidence of glomerular hyperfiltration, regardless of the timing of the diabetes diagnosis in unadjusted models (Fig. 1D). Among participants in the during and after groups, the 12-year incidence of hyperfiltration was 57.2% and 54.2%, respectively, both significantly higher than in the never group (37.1%; *P* = .001 and *P* = .03, respectively). Differences in hyperfiltration between the during vs never groups were maintained after adjusting for sociodemographic factors (Fig. 1D; adjusted *P* = .01), and further adjustment for time-weighted mean HbA_{1c} (*P* = .01).

Table 3 shows cross-sectional associations between maternal history of diabetes groups with markers of retinopathy and cardiovascular measures. Participants in the after group had a greater proportion of retinopathy (≥ very mild nonproliferative diabetic retinopathy; *P* = .04) and a trend for a greater 3-step progression in retinopathy (*P* = .07) compared with the never group in unadjusted models; however, the association disappeared after adjustment for sociodemographic covariates. No associations between maternal diabetes diagnosis and arterial stiffness were observed, but a significant effect of maternal diabetes diagnosis on heart rate variability, with lower SDNN among participants in the during and after vs never groups, was identified. Effects were maintained after adjustment for sociodemographic confounders. However, there were no statistically significant differences according to the timing of maternal diabetes diagnosis.

Discussion

We previously reported that diabetes diagnosis in mothers or both parents was associated with adverse diabetes characteristics at baseline and early follow-up in the TODAY study (13, 14). The present analysis extends these findings to show the effect of parental diabetes on outcomes in youth with T2D over long-term follow-up, demonstrating that parental diabetes history is associated with worse glycemic control and markers of autonomic neuropathy (ie, heart rate variability) in youth-onset T2D. Over up to 12 years of follow-up, we found a greater effect of maternal than paternal diabetes on longitudinal HbA_{1c} levels, β-cell function measures, and cumulative incidence of loss of glycemic control. Offspring of mothers with diabetes had an increased cumulative incidence of glomerular hyperfiltration. The larger effect of maternal than paternal diabetes suggests a possible role for in utero

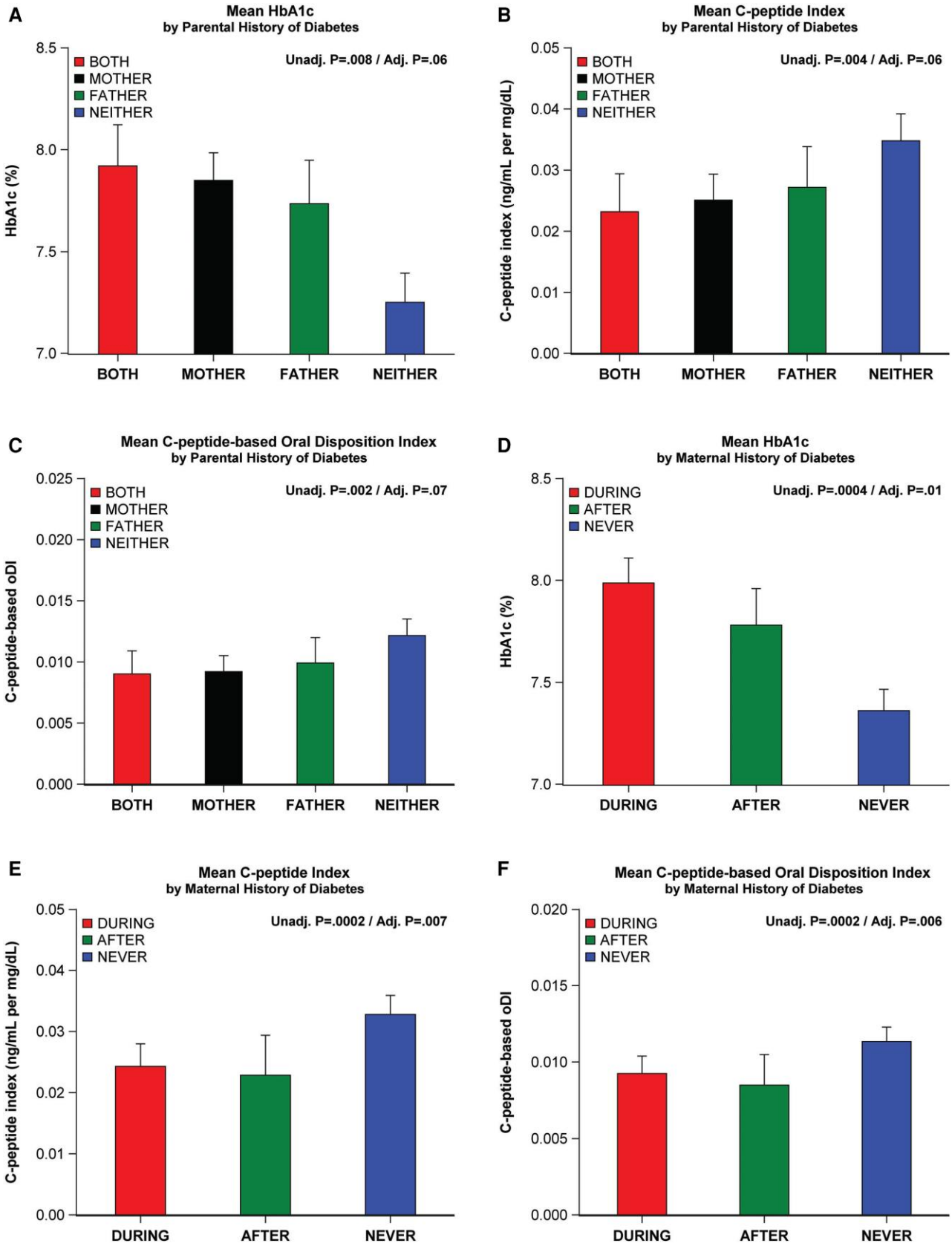

Figure 2. Bar graphs of model-estimated means averaged over 12 years of follow-up of A and C, glycated hemoglobin A_{1c} (HbA_{1c}); B and D, C-peptide index; and C and F, C-peptide-based oral disposition index by parental and maternal history of diabetes group. Model-derived mean estimates ± SE for HbA_{1c} and geometric mean estimates ± SE for C-peptide index and C-peptide–based oral disposition index obtained from unadjusted linear mixed models over 12 years of follow-up are shown in each bar graph. oDI, oral disposition index; ΔC30/ΔG30: increment of C-peptide over increment of glucose during the first 30 minutes of the 75-g oral glucose tolerance test. *P* values shown for unadjusted (Unadj.) and models adjusted (Adj.) for participant age, sex, race-ethnicity, and highest level of household annual income at baseline.

Table 3. Cross-sectional associations between parental and maternal history of diabetes and measures of retinopathy, arterial stiffness, and heart rate variability assessed at study year 12[a]

	Parental history of diabetes						Maternal history of diabetes				
Outcome	Both parents	Mother only	Father only	Neither parent	Unadj. *P*	Adj. *P*	During or before pregnancy	After pregnancy	Never diagnosed	Unadj. *P*	Adj. *P*
Retinopathy[b]	n = 54	n = 103	n = 36	n = 95			n = 136	n = 62	n = 170		
Any NPDR	28 (51.9)	53 (51.5)	20 (55.6)	38 (40.0)	.25	.26	68 (50.0)	37 (59.7)	71 (41.8)	.04	.10
Worsening	14 (25.9)	21 (20.4)	5 (13.9)	19 (20.0)	.56	.55	35 (25.7)	15 (24.2)	27 (15.9)	.07	.19
Cardiovascular[c]	n = 48	n = 100	n = 33	n = 98			n = 126	n = 58	n = 172		
Arterial stiffness, higher values are worse											
Carotid femoral PWV, m/s	6.9 ± 1.2	7.0 ± 1.6	7.1 ± 1.2	7.2 ± 1.9	.83	.58	7.0 ± 1.6	7.2 ± 1.7	7.2 ± 1.9	.56	.36
Change	0.7 ± 1.1	0.7 ± 1.5	0.4 ± 1.2	0.8 ± 2.2	.79	.60	0.8 ± 1.5	0.7 ± 1.9	0.8 ± 2.1	.92	.69
Heart rate variability, lower values are worse											
SDNN, ms	44.4 ± 28.1	40.6 ± 25.6	48.0 ± 27.6	54.5 ± 30.7	.003	.04	41.9 ± 25.5	41.0 ± 26.0	53.5 ± 31.1	.0005	.006
Change	−12.2 ± 24.6	−16.2 ± 29.9	−16.0 ± 28.8	−0.3 ± 24.6	.002	.008	−15.8 ± 26.1	−11.8 ± 27.9	−3.4 ± 27.6	.002	.03
PNN50, %	15.9 ± 21.6	14.4 ± 19.3	19.5 ± 23.7	20.7 ± 21.2	.26	.32	14.1 ± 19.4	16.2 ± 21.5	21.9 ± 23.5	.08	.13
Change	−9.2 ± 22.6	−11.1 ± 21.6	−8.9 ± 20.3	−5.0 ± 19.5	.33	.22	−11.0 ± 20.6	−8.8 ± 23.9	−4.9 ± 22.2	.10	.21

Abbreviations: NPDR, nonproliferative diabetic retinopathy; PNN50, percentage of adjacent NN intervals with a difference greater than 50 ms; PWV, pulse wave velocity; SDNN, SD of normal R-R interval.
[a]N (%) or unadjusted mean ± SD are shown.
[b]Retinopathy data from fundus photo assessment performed around study year 12 with any NPDR defined as mild NPDR or above and worsening retinopathy defined as a 3-step or greater progression in Early Treatment Diabetic Retinopathy Study level between 2 fundus photo assessments evaluated 7 years apart.
[c]Data from vascular assessment performed around study year 12 and change in values based on a 5-year change between 2 vascular assessments. Data at 12 years of follow-up were available for approximately 58% of the participants. *P* value obtained from logistic model for the retinopathy binary outcomes and from general linear regression models for the continuous arterial stiffness outcomes, before (unadjusted *P* values; Unadj.) and after adjustment (Adj.) for participant age, sex, race-ethnicity, and highest level of household annual income at baseline. Heart rate variability values were log-transformed before testing to approximate normality.

programming or epigenetic mechanisms in diabetes complications, though we did not observe differences in outcomes between participants whose mothers were diagnosed with diabetes before/during vs after pregnancy. Although prior analyses have reported effects of maternal diabetes on risk of T2D in youth, our data represent a novel observation that parental diabetes history influences not only T2D onset, but also long-term progression/complications.

There are limited data on the effects of parental diabetes on diabetes progression or complications in youth with T2D. However, in a study of 1473 Greek adults with T2D, those with a history of diabetes in either parent had an earlier age of onset and trends for higher prevalence of dyslipidemia and retinopathy (18). By contrast, our analysis identified an effect of maternal diabetes history on markers of autonomic neuropathy and hyperfiltration, but not with dyslipidemia or retinopathy; although our study population was younger, the reasons for these differences are unclear. Similar effects of parental diabetes diagnosis on age of onset have been reported in prior analyses of baseline characteristics in the SEARCH for Diabetes in Youth cohort (6) and in Pima family studies (19).

Reductions in β-cell function following in utero exposure to diabetes have been reported in other populations. Among Pima families, insulin secretion rates were lower among nondiabetic individuals whose mothers had diabetes diagnosed before pregnancy, as compared to those whose mothers were diagnosed later, suggesting a role of in utero exposure to hyperglycemia (8). Similarly, an analysis of 587 young adults without known diabetes found that offspring of women with gestational or type 1 diabetes mellitus had reductions in the oDI, a measure of insulin secretion (20). Based on evidence from the Hyperglycemia and Adverse Pregnancy Outcome Follow-up (HAPO) Follow-Up Study, associations between maternal hyperglycemia and offspring β-cell dysfunction (DI) are detectable even with mild glucose elevations below the diagnostic threshold for gestational diabetes (21), as observed in our analysis. By contrast, in the Exploring Perinatal Outcomes among Children (EPOCH) Study (n = 445), in utero diabetes exposure (gestational diabetes or type 1 diabetes) was associated with higher Homeostatic Model Assessment Index (HOMA2-IR) and lower Matsuda index (measures of insulin sensitivity), in offspring at ages 10 to 16 years, but not with oDI (22).

Many potential mechanisms may underlie the association between parental diabetes and decreased β-cell function in offspring, including genetics, epigenetic programming, microbiome transmission, or human milk composition. Our study design does not allow us to infer causal mechanisms, but recent studies support the possibility that participants with parental diabetes may have inherited a genetic burden contributing to diminished β-cell function. Recent genome-wide association studies have shown that many genetic variants linked to youth-onset T2D are related to β-cell function (23). However, we observed a stronger effect of maternal (vs paternal) diabetes on offspring glucose metabolism, which would argue against a purely genetic mechanism. The stronger association between maternal diabetes and metabolic phenotype may reflect the effect of the in utero environment, or the mitochondrial genome, which is maternally inherited. Indeed, evidence in animal and human models has shown that features of the prenatal environment, including hyperglycemia, insulin resistance, or nutrient overload, induce epigenetic and metabolic adaptations that increase risk of chronic diseases, including T2D, in offspring (2, 24). Potential mechanisms include altered stem cell function, increased lipogenesis in liver and adipose tissue, and defects in insulin secretion and β-cell development (25). Moreover, the differences in birth weight we observed across parental diabetes categories (ie, higher birth weight in offspring of mothers with diabetes, lower birth weight in offspring of fathers with diabetes) suggest the possibility that differences in fetal growth may contribute to altered β-cell function and glycemia, consistent with previous reports that both low birth weight and large birth weight infants are at risk for future T2D (25).

The shared postnatal environment, including diet, physical activity patterns, the microbiome, and the ecological exposome, may also contribute to the relationship between parental diabetes and offspring diabetes phenotype. Environmental toxins have been associated with risk of T2D (26), with a disproportionate effect on historically marginalized groups (27). A potential role for social determinants was suggested in our analysis, as household income was lowest for families in which both parents had diabetes. Other external factors, including the built environment and food access, have also been associated with T2D and might play a role in intergenerational diabetes risk (28, 29). We controlled for social determinants of health in our analyses by including sociodemographic characteristics in the regression models. Importantly, we found that longitudinal associations between maternal diabetes diagnosis and loss of glycemic control, β-cell function, HbA_{1c}, hyperfiltration, and autonomic neuropathy measures persisted in adjusted analyses, whereas effects on microvascular outcomes were attenuated, suggesting that social determinants may mediate some of the observed effects on diabetes microvascular complications.

Strengths of this study include the large cohort, high retention rate, and long duration of follow-up into adulthood, allowing assessment of the progression of youth-onset diabetes and incidence of complications over time. There were detailed, standardized clinical assessments for measurements of glycemic control and complications. Our analyses adjusted for confounders and key covariates. We do acknowledge areas deserving further investigation. While our study shows clear associations between parental diabetes and outcome measures, we are unable to determine the mechanisms driving these effects. We relied on parental report of diabetes diagnosis, potentially misclassifying parents with undiagnosed diabetes and misclassification of timing of diagnosis in relation to pregnancy. We also could not capture nondiabetic levels of hyperglycemia during pregnancy that may have preceded a later diabetes diagnosis in mothers. While we report maternal BMI at enrollment, we did not have maternal BMI during pregnancy or data on paternal BMI. An additional limitation is that household income at baseline differed according to parental diabetes categories. Although it is reassuring that associations between maternal diabetes and offspring diabetes characteristics were maintained after adjustment for highest level of household income, there remains a possibility of residual confounding by other factors related to socioeconomic status. Last, while diabetes care was provided to all participants during the randomized controlled trial period in the first 2 to 6 years of the study, participants obtained diabetes care in the community during the latter stages of the study, raising the possibility that

differences in access and quality of care may have contributed to some of the observed associations.

Our data, from a uniquely well-characterized cohort, demonstrate the effect of parental diabetes on the trajectory of youth-onset diabetes into young adulthood. Maternal diabetes, regardless of diagnosis before or after pregnancy, is associated with poor diabetes control, reduced β-cell function, glomerular hyperfiltration, and increased risk of autonomic dysfunction in offspring with youth-onset of T2D. Further investigations to determine mechanisms of these findings, and identify targets for intervention, are needed to reduce or halt this intergenerational transmission.

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Author Contributions

R.D.S. and E.I. designed the analyses and wrote the manuscript; L.E. and B.T. conducted the statistical analyses, prepared the tables and figures, and wrote parts of the manuscript; S.C., M.E.G., J.K., M.MK., R.F., J.B.T., and M.V. contributed to the interpretation of data, reviewed, and edited the manuscript; R.D.S., E.I., and L.E. had full access to all data in the study and take responsibility for the integrity and accuracy of the data analysis.

Disclosures

The authors have nothing to disclose.

Data Availability

The data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

Clinical Trial Information

ClinicalTrials.gov number NCT00081328 (registered January 1, 2002).

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