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The Influence of Exposure to Maternal Diabetes *In Utero* on the Rate Of Decline in Beta-Cell Function Among Youth with Diabetes

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Abstract

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Author Contributions

T.C. advised on analysis, wrote the manuscript; J.A. conducted the analysis, reviewed/edited the manuscript; R.D. Jr. advised on analysis, reviewed/edited the manuscript; D. P. reviewed/edited the manuscript; E.M. reviewed/edited the manuscript; J.L. reviewed/edited the manuscript; L.D. reviewed/edited the manuscript; J.L. reviewed/edited the manuscript; S.S. reviewed/edited the manuscript; C.G. reviewed/edited the manuscript; B.R. reviewed/edited the manuscript; D.D, advised on analysis, contributed to the discussion, reviewed/edited the manuscript.

A relationship between exposure to maternal diabetes *in utero* and a younger age at diagnosis of type 2 diabetes was detected in SEARCH for Diabetes in Youth Study, while no significant association was detected with paternal diabetes status, suggesting an independent effect of the intrauterine exposure to hyperglycemia. We assessed the influence of exposure to maternal diabetes *in utero* on beta cell decline measured using fasting C-peptide (FCP) among 1079 youth with diabetes, including 941 with type 1 and 138 with type 2, who were followed post-diagnosis for an average of 58 months. No significant relationship was detected between exposure to maternal diabetes *in utero* and change in FCP levels in youth with type 1 or type 2 diabetes. These findings suggest that exposure to maternal diabetes *in utero* may not be an important determinant of short-term beta-cell function decline in youth with type 1 or type 2 diabetes.

Keywords

Gestational diabetes; fetal overnutrition; fetal exposure to diabetes; childhood type 2 diabetes; type 1 diabetes; diabetes during pregnancy; beta-cell function; fasting C-peptide

Introduction

A relationship between exposure to maternal diabetes *in utero* and increased risk of type 2 diabetes in the offspring has been reported among diverse populations in the United States (1–3) and Europe (4;5). Within the Pima Indian population, siblings born after their mother had been diagnosed with type 2 or gestational diabetes mellitus (GDM) had a threefold risk of developing type 2 diabetes than siblings born before the diagnosis (2). Results from the SEARCH Case-Control Study indicate that non-Hispanic white, Hispanic and African American youth with type 2 diabetes were 5.7 times more likely to have been exposed to maternal diabetes *in utero* (mostly GDM) than controls (95%CI: 2.4–13.4, $p<0.0001$) (6). A study by Clausen et al. (4) of Caucasian young adults in Denmark found that more than 20% of offspring born to mothers with GDM and 10% of offspring born to mothers with type 1 diabetes had type 2 or pre-diabetes by the age of 22, suggesting a predisposition that is independent of maternal diabetes type. Moreover, the SEARCH study has reported that, among youth with type 2 diabetes, exposure to maternal diabetes *in utero* was associated with 1.68 year younger age at diagnosis (7) ($p=0.018$) while there was no significant association with paternal diabetes status ($p=0.853$), suggesting an independent effect of the intrauterine exposure to hyperglycemia that extends beyond shared genetic and environmental factors. However, a relationship between age at diagnosis and *in utero* exposure to maternal diabetes was not detected for youth with type 1 diabetes.

Animal studies have demonstrated hyperplasia and hyperactivity of pancreatic beta cells in offspring of diabetic pregnancies (8–10). However, there are no epidemiologic data in human populations exploring whether exposure to maternal diabetes *in utero* influences beta-cell function at diagnosis and the subsequent rate of beta-cell function decline in children with diabetes. We used data from the SEARCH for Diabetes in Youth Study to test the hypothesis that exposure to maternal diabetes *in utero* will be associated with a faster rate of decline in fasting C-peptide (FCP) levels after diabetes diagnosis among youth with type 2, but not in those with type 1 diabetes.

Methods

Data for these analyses come from the SEARCH for Diabetes in Youth prospective cohort study. A detailed description of the SEARCH study methods has been published elsewhere(11). Briefly, SEARCH has been conducting population-based ascertainment of youth and young adults with newly diagnosed (incident) diabetes starting in 2002 and continuing through the present. SEARCH recruited participants from four geographically defined populations in Ohio, Colorado, South Carolina and Washington, as well as from Indian Health Service beneficiaries of several American Indian populations, and enrollees in several managed health care plans in California and Hawaii. Participants with newly diagnosed diabetes from 2002 through 2005 were invited to participate in a baseline research visit and follow up exams at approximately 12, 24, and 60 months after their baseline visit. At each research visit fasting blood samples were obtained from metabolically stable participants (defined as no episode of diabetic ketoacidosis during the previous month), physical measurements were collected, and questionnaires were administered. The study was reviewed and approved by the local Institutional Review Board(s) that had jurisdiction over the local study population and all participants provided informed consent and/or assent.

Measurement

Study visits occurred after an eight hour overnight fast. Participants did not take diabetes medicines the morning of the visit, and long-acting insulin was administered the evening before the visit and then discontinued. For youth aged ≥ 3 years, a brief physical examination was conducted including measurement of weight and height using standardized procedures and used to calculate body mass index (BMI [kg/m^2]). Age- and sex-specific BMI *z*-scores were calculated using growth charts with a SAS program available from the Centers for Disease Control and Prevention (12). Waist circumference was measured using NHANES III protocol(13). Race and ethnicity were self-reported using 2000 US Census questions (14) and classified as Hispanic, non-Hispanic white (NHW), non-Hispanic black (NHB), American Indian (AI), and Asian/Pacific Islander (API). For these analyses, race/ethnicity was categorized as NHW and other than non-Hispanic white, including all other racial/ethnic groups.

Fasting blood samples were used to analyze diabetes autoantibodies (DA), hemoglobin A1C (A1C) and fasting C-peptide (FCP). Assays were performed at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, the Central Laboratory for SEARCH. Glutamic acid decarboxylase-65 (GADA) and insulinoma-associated-2 (IA-2A) autoantibodies were analyzed using a standardized protocol and a common serum calibrator developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored standardization group (15). The cutoff values for positivity were 33 NIDDKU/ml for GAD65 and 5 NIDDKU/ml for IA2 (15). For this report, type 1 diabetes was defined as presence of a provider diagnosis of type 1 diabetes plus DA positivity at the baseline visit (either GADA or IA-2A), while type 2 diabetes was defined as a provider diagnosis of type 2 diabetes and absence of DA positivity. A1C (%) was measured in whole blood with an automated nonporous ion-exchange high-performance liquid chromatography system (model G-7; Tosoh Bioscience, Montgomeryville,

Pennsylvania). Levels of FCP were determined by a two-site immunoenzymetric assay (Tosoh AIA, Tosoh Bioscience Inc., San Francisco, CA). The assay sensitivity is 0.05 ng/ml.

Presence of diabetes in the biological mother and the age of diagnosis were obtained by self-report from the participant or their parent. Information on maternal diabetes type was not collected. Study participants whose mothers had diabetes were classified based on the timing of the mother's diagnosis relative to the subject's birth. Classification of exposure to diabetes *in utero* among SEARCH study has been reported previously(7). Subjects whose mothers had diabetes before their birth were classified as "exposed to *in utero* diabetes". Subjects whose mothers did not have diabetes or who were diagnosed after the birth of the index child were classified as "unexposed". Subjects who had missing data on mother's diabetes status or timing of diagnosis were excluded from this analysis.

Study Participants

The study population consisted of SEARCH participants with type 1 or type 2 diabetes who were newly diagnosed from 2002 through 2005, had at least two longitudinal measurements of FCP levels, and had complete questionnaire data to determine a history of *in utero* exposure to diabetes. A total of 941 youth with type 1 and 138 youth with type 2 met these requirements, for a total of 1079 participants. Subjects with incomplete or missing questionnaire data to determine *in utero* diabetes exposure were excluded (N=198). Youth whose diabetes type or DA status were missing, youth with type 1 diabetes who were DA negative and youth with type 2 diabetes who were DA positive were also excluded (N=295).

Data Analysis

Comparisons of baseline participant characteristics, by *in utero* exposure to diabetes, were performed using t-tests for continuous variables, and chi-square tests or Fisher's exact test for categorical variables, stratified by diabetes type. To explore differences in the short-term rate of change in FCP levels by exposure to maternal diabetes *in utero*, mixed effects linear models accounting for within subject correlation were used to model the rate of change in FCP levels, stratified by diabetes type, and adjusted for sex, race/ethnicity (non-Hispanic white vs. Other), age at diagnosis, clinic, parental education (<high school vs. ≥ high school), total household income (<$25,000 vs. ≥$25,000/year), BMI Z-score, and A1C. Due to a skewed distribution of FCP levels, values were log-transformed for these analyses. Predicted FCP rate of change was expressed as percent change in FCP level per month and 95% confidence interval. An interaction term between duration of disease and exposure to maternal diabetes *in utero* was the main covariate of interest. A supplemental model combined youth with type 1 and type 2 diabetes and tested a 3-way interaction between diabetes type, exposure to maternal diabetes *in utero*, and duration of disease to determine if the effect of exposure on change in log-transformed FCP over time was modified by diabetes type. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA). Results were considered significant if $p < 0.05$.

Results

Characteristics of study participants with type 2 and type 1 diabetes, according to exposure to maternal diabetes *in utero*, appear in Table 1. Exposure to maternal diabetes *in utero* occurred in 14.5% of youth with DA negative, type 2 diabetes and 1.8% of youth with DA positive type 1 diabetes. As reported previously (7), youth with type 2 diabetes who were exposed to maternal diabetes *in utero* had a younger age (years) at diagnosis (11.3 ± 2.1 vs. 13.7 ± 2.3, p<.0001) and, therefore, were younger (years) at the baseline visit (12.5 ± 2.1 vs. 15.0 ± 2.3, p<.0001) than those not exposed. However, for both youth with type 2 and type 1 diabetes, other participant characteristics, including sex, race/ethnicity, parental level of education, total household income, paternal history of diabetes status, were not significantly different for those unexposed and exposed to maternal diabetes *in utero*. In addition, participant characteristics at the baseline visit including FCP levels, BMI *z*-score, and A1C, were not significantly different by exposure status for youth with type 2 or type 1 diabetes.

Table 2 shows the predicted FCP levels of SEARCH participants with type 2 and type 1 diabetes according to *in utero* exposure status from the type-stratified longitudinal linear mixed model adjusted for age at diagnosis, sex, race/ethnicity, clinic, parental education, household income, BMI *z*-score, and A1C. No significant differences were detected in predicted FCP levels by *in utero* exposure to maternal diabetes among either youth with type 2 or type 1 diabetes. For youth with type 2 diabetes, model predicted FCP levels at 6-months post diagnosis were 3.53 ng/ml (95%CI: 3.04, 4.10) vs. 2.94 ng/ml (95%CI: 2.30, 3.74) for the unexposed and exposed, respectively. At 30 months post diagnosis, youth with type 2 diabetes had a model predicted FCP level of 3.18 ng/ml (95%CI: 2.74, 3.70) among the unexposed and 2.65 ng/ml (95%CI: 2.08, 3.38) among those exposed to maternal diabetes *in utero*. Adjustment for the age at onset of diabetes in exposed youth did not have an appreciable effect on estimates. For youth with type 1 diabetes, the predicted FCP levels at 6-month post diagnosis were 0.54 ng/ml (95%CI: 0.48, 0.62) vs. 0.63 ng/ml (95%CI: 0.46, 0.86) for the unexposed and exposed, respectively. Youth with type 1 diabetes had an appreciable decline at 30 months post-diagnosis, but the predicted FCP levels were similar in unexposed [0.26 ng/ml (95%CI: 0.22, 0.29)] and exposed youth [0.29 ng/ml (95%CI: 0.21, 0.41)].

Figure 1 shows the estimated decline in FCP levels over time among youth with type 2 and type 1 diabetes by exposure to maternal diabetes *in utero* from the type-stratified longitudinal linear mixed effect models. The estimated monthly rate of change in FCP levels was −0.43% (95%CI: −0.17, −0.69) among youth with type 2 and −3.11% (95%CI: −3.00, −3.21) among youth with type 1 diabetes. The rate of change in beta cell function was not significantly different by exposure to maternal diabetes *in utero* for youth with type 2 (p=0.16) or type 1 diabetes (p=0.90). Overall, exposure to diabetes *in utero* was associated with 17% lower FCP levels among youth with type 2 diabetes (95% CI: −34%,+6%) and 15% higher FCP levels for youth with type 1 diabetes (95% CI: −14%, +55%), although these differences were not statistically significant (p=0.13 and p=0.35, respectively). Finally, in the model combining youth with type 1 and type 2 diabetes, the effect of exposure to maternal diabetes *in utero* on beta cell rate of change was not significantly modified by youth diabetes type (p=0.41).

Discussion

This study found no evidence that exposure to maternal diabetes *in utero* is associated with the beta cell function soon after diagnosis or the decline in beta-cell function in the first few years following diagnosis among youth with type 1 or type 2 diabetes. Although in this sample of SEARCH cohort study participants *in utero* exposure to maternal diabetes was associated with younger age at diagnosis with type 2 diabetes, confirming previous findings in the larger SEARCH study (7), exposure to maternal diabetes was not a significant predictor of beta cell function at baseline or short-term beta cell decline in these youth.

A limited number of studies have explored factors associated with beta cell decline in youth with either type 2 or type 1 diabetes and, to our knowledge, none have specifically assessed the effect of exposure to diabetes in utero on beta cell decline following diagnosis of diabetes. Both animal and human studies suggest an adverse influence of maternal diabetes on fetal beta-cell function which may contribute to development of type 2 diabetes(16–20). *In utero* exposure to maternal diabetes in a streptozotocin (STZ)-induced rat model results in changes to the morphology, number and size of offspring islets, with impaired insulin secretion (16;17). At 15-weeks, isolated islets from rat offspring exposed to STZ-induced maternal diabetes showed low insulin secretion in response to a high (16 mM) glucose challenge, compared to control rats. Studies in humans are limited, but suggest that exposure to maternal hyperglycemia *in utero* results in impaired insulin secretion (21), leading to impaired glucose tolerance later in life (22;23). Among Pima Indian adults the acute insulin response to infused glucose was 40% lower in individuals whose mothers had diabetes during pregnancy than in those whose mothers developed diabetes after the birth of the subject (22).

Although small studies have suggested that youth with type 2 diabetes have some degree of beta-cell dysfunction at diagnosis (24;25), there are no large prospective studies of the natural evolution and determinants of beta-cell function in youth with type 2 diabetes. The situation is even more complex given the lack of a standardized definition of type 2 diabetes in youth. A study of 66 children with provider-defined type 2 diabetes at the Children's Hospital of Philadelphia (26) found that FCP levels at diagnosis were significantly lower in youth who presented in diabetic ketoacidosis (DKA)(1.08 ng/ml versus 3.04 ng/ml when DKA was absent). Although the rate of decline in FCP levels was not assessed in this study, the authors hypothesized an initial slow decline in the first years following diagnosis, followed by a steeper one with longer duration. In contrast, among youth with autoimmune diabetes, several clinical trial studies reported a 50% decline in the first year post-diagnosis (27–30). Our data in a selected sample of SEARCH cohort study participants are consistent with previous studies reporting a very slow progression of beta-cell dysfunction in youth with antibody negative, type 2 diabetes (0.4% decline per month) and a steeper decline in those with antibody positive type 1 diabetes (3.1% per month) during the first few years following diabetes diagnosis.

We found that short-term decline in beta cell function was not significantly associated with exposure to maternal diabetes *in utero* for youth with type 2 or type 1 diabetes. Our findings suggest that the onset and progression of disease among youth with type 1 diabetes is little,

if any, affected by exposure to maternal diabetes during the intrauterine life (in fact overall FCP levels were somewhat higher in exposed youth). However, among youth with type 2 diabetes, the decline in beta cell function is likely to be more gradual (26) and, although we did not find a significant association between exposure to diabetes *in utero* and rate of change in FCP levels in the first few years post-diagnosis, a time when there is little beta-cell loss, our study findings cannot rule out an impact on longer-term decline of beta cell decline. Therefore, longer follow-up of youth with type 2 diabetes is needed to conclusively address this issue.

Our study has several limitations including the use of FCP rather than stimulated C-peptide to assess baseline and change in beta cell function over time. However, FCP has been previously reported to correlate well with stimulated C-peptide (31–33). Exposure was defined by self-report of maternal diabetes status and time of diagnosis. Self-report was provided by parents for younger subjects and by the subjects themselves for those who are older. It is possible that parents were more likely to accurately report the timing of maternal diagnosis than the subjects themselves therefore leading to some misclassification among older subjects. Since such misclassification is unlikely to be differential by offspring beta cell function at follow up, it would result, if present, in a bias toward the null. An additional limitation is the small sample of youth exposed to diabetes *in utero* (20 exposed with type 2 diabetes, 17 exposed with type 1 diabetes), so some of the non-significant associations, particularly among youth with T2D, may have been the result of the small sample. However, SEARCH is one of the largest studies of type 2 diabetes in youth conducted to date including both assessment of both longitudinal change in FCP and *in utero* exposure to maternal diabetes. Our study has other important strengths including the use of a well characterized sample of youth with both type 1 and type 2 diabetes whose diabetes type was carefully defined based on both provider assessment and measurement of DA at baseline visit, and careful collection of exposure data.

This study suggests that exposure to maternal diabetes *in utero* is not significantly associated with in the short-term post-diagnosis progression of beta-cell dysfunction in youth with type 1 or type 2 diabetes. Nevertheless, our results call for larger studies, as well as longer term follow up of youth with type 2 diabetes, to conclusively assess the long-term effects of *in utero* exposure on beta-cell function in this population.

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Abbreviations

FCP	fasting C-peptide
NHW	non-Hispanic white
NHB	non-Hispanic Black
AI	American Indian
API	Asian/Pacific Islander
GDM	gestational diabetes mellitus
DA	diabetes autoantibody
GADA	Glutamic acid decarboxylase-65 autoantibody
IA-2A	insulinoma-associated-2 autoantibody
STZ	streptozotocin

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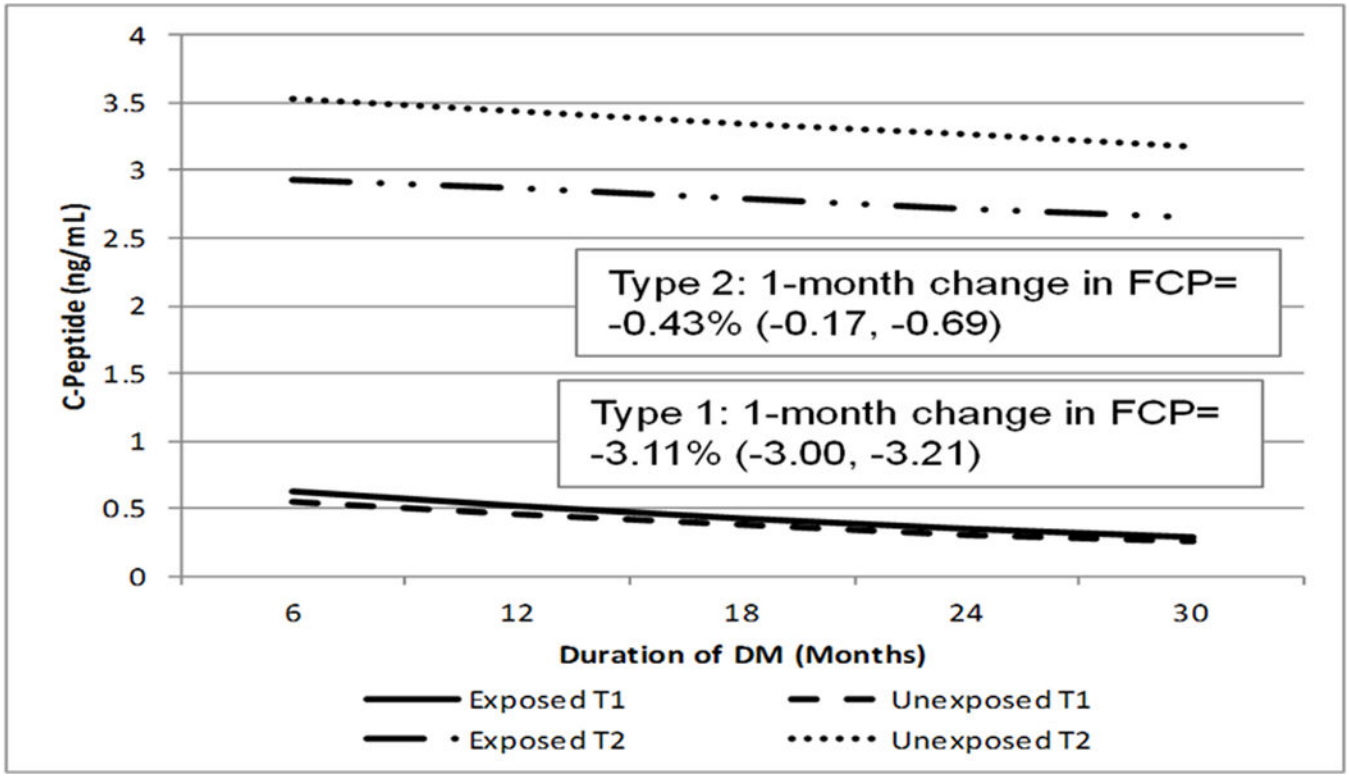

Figure 1.

Overall FCP levels* according to exposure to maternal diabetes *in utero* in youth with type 2 and type 1 diabetes

*Type-stratified models adjusted for sex, race, age at diagnosis, clinic, parental education, household income, in utero exposure to maternal diabetes, baseline BMI z-score, and A1C.

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Table 1

Characteristics of youth with diabetes in SEARCH study at baseline visit, according to exposure to diabetes *in utero*: mean ± SD or N (%)

	Participants with Type 2 Diabetes			Participants with Type 1 Diabetes		
	Unexposed (N=118)	**Exposed (N=20)**	**P-value***	**Unexposed (N=924)**	**Exposed (N=17)**	**P-value***
Age at diagnosis (years)	13.7 ± 2.27	11.3 ± 2.08	<0.0001	9.5 ± 3.91	8.1 ± 4.07	0.12
Duration of diabetes at baseline visit(months)	11.5 ± 7.42	9.0 ± 3.69	0.02	9.4 ± 6.12	9.4 ± 7.21	0.98
Baseline visit age (years)	15.0 ± 2.32	12.5 ± 2.12	<0.0001	10.8 ± 3.93	9.3 ± 4.25	0.13
Female sex	74 (62.71)	13 (65.00)	0.85	457 (49.46)	9 (52.94)	0.78
Non-white race/ethnicity	91 (77.12)	17 (85.00)	0.56**	199 (21.54)	3 (17.65)	1.00**
Baseline BMI *z*-score	2.17 ± 0.61	2.17 ± 0.56	0.99	0.55 ± 0.96	0.50 ± 1.09	0.81
Baseline A1c (% NGSP) IFCC (mmol/mol)	6.9 ± 2.01, 51.9 ± 22.0	7.2 ± 1.90; 55.2 ± 20.8	0.50	7.6 ± 1.39; 59.6 ± 15.2	7.8 ± 1.24 61.7 ± 13.6	0.72
Baseline Fasting C-peptide (ng/ml)	4.00 ± 2.05	3.79 ± 2.09	0.66	0.67 ± 0.66	0.59 ± 0.44	0.60
Parent education: high school or more	103 (87.29)	16 (80.00)	0.48**	889 (96.42)	17 (100)	1.00**
Total household income ≥$25,000/year	58 (54.72)	8 (40.00)	0.23	760 (87.66)	13 (76.47)	0.25**
Paternal history of diabetes	26 (24.07)	4 (23.53)	1.00**	65 (7.21)	1 (5.88)	1.00**

* P-value from Chi-square or Fisher's exact test for categorical variables and t-test for continuous variables

** Fisher's exact test used in place of Chi-square due to low expected cell counts

Table 2

Fasting c-peptide levels* of SEARCH participants since the diagnosis of diabetes according to exposure to maternal diabetes *in utero*

	Type 2 FCP (ng/ml) 95% CI		Type 1 FCP (ng/ml) 95% CI	
	Unexposed	**Exposed**	**Unexposed**	**Exposed**
6-months	3.53 (3.04, 4.10)	2.94 (2.30, 3.74)	0.54 (0.48, 0.62)	0.63 (0.46, 0.86)
9-months	3.48 (3.00, 4.04)	2.90 (2.28, 3.69)	0.50 (0.43, 0.57)	0.57 (0.41, 0.79)
30-months	3.18 (2.74, 3.70)	2.65 (2.08, 3.38)	0.26 (0.22, 0.29)	0.29 (0.21, 0.41)

*LSmeans adjusted for sex, race, age at diagnosis, clinic, parental education, household income, baseline BMI z-score, and A1C