Long-term Cognitive Implications of Intrauterine Hyperglycemia in Adolescent Offspring of Women With Type 1 Diabetes (the EPICOM Study)

Birgitte Bytoft,[1,2,3] Sine Knorr,[4,5] Zuzana Vlachova,[6,7] Rikke B. Jensen,[3,8] Elisabeth R. Mathiesen,[1,3,9] Henning Beck-Nielsen,[6] Claus H. Gravholt,[4,5] Dorte M. Jensen,[6,7,10] Tine D. Clausen,[11] Erik L. Mortensen,[12] and Peter Damm[1,2,3]

Diabetes Care 2016;39:1356–1363 | DOI: 10.2337/dc16-0168

OBJECTIVE

Exposure to maternal diabetes in utero may have a negative impact on the developing brain. The objective was to examine long-term cognitive consequences of intrauterine hyperglycemia in adolescent offspring of women with type 1 diabetes and to ascertain a possible association with maternal HbA_{1c}.

RESEARCH DESIGN AND METHODS

Offspring of a prospectively followed cohort of women with type 1 diabetes (*n* = 277) participated in a follow-up examination at the age of 13–19 years. A control group from the background population was identified (*n* = 301). Cognitive function was evaluated using Reynolds Intellectual Assessment Scales and classified into indices of composite intelligence, verbal and nonverbal intelligence, and composite memory. Frequencies of reading and writing problems and attendance to classes for children with learning difficulties were assessed.

RESULTS

Offspring of women with type 1 diabetes scored lower in all normalized and standardized intelligence indices compared with controls: composite intelligence (95.7 vs. 100, *P* = 0.001), verbal intelligence (96.2 vs. 100, *P* = 0.004), nonverbal intelligence (96.4 vs. 100, *P* = 0.008), and composite memory (95.7 vs. 100, *P* = 0.001). A higher frequency of diabetes-exposed offspring had parent-reported learning difficulties in primary school. Differences between groups remained after adjustment for confounders and potential mediators. We found no direct association between maternal HbA_{1c} and offspring cognitive function in the exposed group.

CONCLUSIONS

Adolescent offspring of women with type 1 diabetes had lower cognitive function compared with a control group, also after adjustment for confounders and potential mediators. These differences may reflect direct harmful effects of maternal diabetes on neurodevelopment in the offspring.

[1]*Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark*
[2]*Department of Obstetrics, Rigshospitalet, Copenhagen, Denmark*
[3]*Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
[4]*Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark*
[5]*Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark*
[6]*Department of Endocrinology, Odense University Hospital, Odense, Denmark*
[7]*Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*
[8]*Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark*
[9]*Department of Endocrinology, Rigshospitalet, Copenhagen, Denmark*
[10]*Department of Gynecology and Obstetrics, Odense University Hospital, Odense, Denmark*
[11]*Department of Gynecology and Obstetrics, Nordsjaellands Hospital, Hilleroed, Denmark*
[12]*Section of Environmental Health, Department of Public Health and Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark*

Corresponding author: Birgitte Bytoft, birgitte.bytoft@regionh.dk.

Received 27 January 2016 and accepted 17 May 2016.

Clinical trial reg. no. NCT01559181, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0168/-/DC1.

Intrauterine hyperglycemia has both short-term and long-term implications on offspring morbidity and mortality, which are associated with the degree of maternal glycemic control before and during pregnancy (1–9).

Development of the central nervous system is an array of complex processes, initiated in the early embryonic period continuing until late adolescence and adulthood (10). These processes are known to be vulnerable to a large number of adverse environmental factors associated with an increased risk of neurological and psychiatric disorders in later life (11–16).

A hyperglycemic intrauterine environment may exert a negative impact on development of the fetal brain, with long-term implications for cognitive function. This association may reflect a direct harmful influence of hyperglycemia and/or the effects of potential mediators associated with maternal diabetes in pregnancy: preterm birth and complications in pregnancy, at delivery, and in the neonatal period. Episodes of severe hypoglycemia or ketoacidosis may also be harmful to the offspring brain.

The potential association between maternal diabetes and cognitive function in the offspring has been investigated in previous studies (17–26). However, these studies are based on diverse populations with diabetes with different follow-up times and various assessments of cognitive function, resulting in diverging conclusions. Some studies report a negative association, with lower scores in cognitive tests and lower school performance (18,22,24), while others find no association after adjustment for confounders (17,20,23) or even a positive association (21,25,26). A Danish register study found no difference in academic achievement in primary school between offspring exposed to maternal type 1 diabetes (n = 707) and matched control subjects (n = 60,341), although a negative association between maternal HbA_{1c} in pregnancy and academic achievement in offspring exposed to maternal diabetes was reported (19).

In this study we performed a follow-up examination of adolescent offspring of a well-characterized cohort of Danish women with type 1 diabetes to assess the cognitive function compared with a control group in order to evaluate the long-term cognitive consequences of intrauterine hyperglycemia. We used measurements of maternal HbA_{1c}, before and during pregnancy, as well as episodes of severe hypoglycemia and ketoacidosis, to evaluate potential associations between maternal metabolic control and cognitive function in the diabetes-exposed offspring.

RESEARCH DESIGN AND METHODS

EPICOM (EPIgenetic, genetic and environmental effects on COgnitive and Metabolic functions in offspring of mothers with type 1 diabetes) is a Danish prospective nationwide follow-up study focusing on the long-term effects of intrauterine hyperglycemia (9). During 1993–1999 all pregnant women with type 1 diabetes in Denmark were prospectively reported to a central register in the Danish Diabetes Association (n = 1,215) (1). The women delivered at one of eight centers responsible for antenatal care and delivery of pregnant women with diabetes in Denmark at that time. Data on maternal demography, diabetes status, and pregnancy outcome were reported to the register after delivery. All deliveries after 24 gestational weeks were included. The coverage of reported pregnancies in women with type 1 diabetes in Denmark in this period was 75–93%.

Participants

The offspring of women with type 1 diabetes in the register with available data were invited to participate in a follow-up examination at the age of 13–19 years (Supplementary Fig. 1). Only singletons and one child per mother were invited (n = 746). With 452 nonrespondents/declines to participate and exclusion of sixteen adolescents, a total of 278 adolescent offspring of women with type 1 diabetes participated (index group). Exclusions were because of maternal diagnosis of type 1 diabetes reclassified to maturity-onset diabetes of the young or type 2 diabetes (n = 12), no contact between mother and child (n = 2), drug abuse (n = 1), and pregnancy (n = 1). We identified a control group through the Danish Central Civil Registration System, matched according to sex, age, and postal code (marker of socioeconomic status) (n = 1,920). A total of 303 participated, and 1,609 did not respond or declined to participate. Eight offspring were excluded for the following reasons: adopted child (n = 4), birthplace outside of Denmark (n = 1), or the obstetric record revealed gestational diabetes mellitus (n = 3). The cognitive tests were completed by 277 (37.1%) exposed and 301 (15.7%) unexposed offspring. Details about the inclusion process and follow-up have recently been published (9).

The protocol was in accordance with the Declaration of Helsinki and approved by the local ethics committee (M-20110239). Written informed consent was obtained from all participants or their parents if the participant was younger than 18 years.

At Follow-up

The participants were examined at one of three Danish University Hospitals (Copenhagen, Odense, and Aarhus) from April 2012 to October 2013. We used Reynolds Intellectual Assessment Scales (RIAS) to evaluate cognitive function. RIAS were selected for their short administration time (30–40 min) and the possibility of applying the same test to all participants, since RIAS are normed in the ages from 3 to 94 years. RIAS constitute a valid test of intelligence and memory with adequate correlation with Wechsler's Intelligence Scale for Children and Wechsler's Adult Intelligence Scale (27,28).

RIAS consist of two verbal and two nonverbal subtests, providing estimates of verbal and nonverbal intelligence. Age-adjusted scores from all four subtests are summed to derive a measure of composite intelligence. Composite memory was assessed using two supplementary RIAS subtests. For ease of interpretation, test scores were normalized and standardized to a mean of a 100 and an SD of 15 in the control group. Cognitive function was evaluated by exposure-blinded testers. Prior to the follow-up examination parents or parents and offspring together completed a questionnaire about learning difficulties in primary school and parental education.

Variables

Outcomes and Exposure

Primary outcomes were composite, verbal, and nonverbal intelligence and composite memory assessed by RIAS. Secondary outcomes were learning difficulties in primary school, assessed by parent-reported

reading and writing problems and attendance in classes for children with learning problems in Danish or mathematics at any time in primary school.

Exposure was maternal type 1 diabetes in fetal life.

Maternal Predictors

We used measurements of HbA_{1c} (preconceptional and first, second, and third trimester) to evaluate maternal glycemic control during pregnancy. Episodes of severe hypoglycemia in pregnancy were defined as hypoglycemia requiring assistance from another person. The definition of ketoacidosis in pregnancy was an event of plasma bicarbonate $<$15 mmol/L and hospitalization. Information about glycemic control and glycemic events was taken from the register in the Danish Diabetes Association (1).

Parental educational level was estimated from the questionnaire completed by the offspring and their parents. It was calculated as the sum of maternal and paternal years in school and in higher education.

Maternal age at delivery, parity, and information about complications in pregnancy were retrieved from the Danish Diabetes Association register (index group) or from obstetric records (control group). Pregnancy complications were defined as occurrence of hydramnios (clinical diagnosis) or preeclampsia (blood pressure $>$140/90 mmHg and proteinuria).

Information on smoking in pregnancy and parental intelligence was not available. In addition we were not able to collect sufficient data on mode of delivery in the control group, and these variables were not included in our analysis.

Offspring Predictors

Data about gestational age, birth weight, congenital malformations, and neonatal complications were extracted from the register (index group) or from obstetric records (control group). Neonatal complications were combined and defined as hypoglycemia (clinical signs that disappeared after administration of glucose), jaundice (treated with phototherapy), respiratory distress (need for assisted ventilation, continuous positive airway pressure $>$1 h after birth), Apgar 5 $<$7, and systemic infections (systemic antibiotics). Birth weight SD scores (bwSDS) were calculated using intrauterine growth curves adjusted for gestational age and sex (29).

Potential Mediators and Confounders

Potential confounders were offspring sex, age at follow-up, parity, parental educational length, and maternal age at delivery. Gestational age, bwSDS, pregnancy complications, and neonatal complications were considered potential mediators between intrauterine hyperglycemia and offspring cognitive function.

Statistics

Normally distributed continuous data are presented as mean and SD. Continuous data with skewed distribution are presented as median and interquartile range. Student *t* test and Mann-Whitney, χ^2, and Fisher exact tests were used to compare groups where appropriate.

For adjustment for the effect of confounders and mediators on offspring cognitive function, multivariate linear regression analyses were performed, with exposure as the independent variable and composite intelligence and composite memory as outcome measures. The results are presented as regression coefficients (β) corresponding to the mean difference in cognitive test score between groups with 95% CI.

Multivariate logistic regression analyses were performed when the outcome measures were learning difficulties. Results were reported as odds ratio (OR) and 95% CI.

We fitted a simple linear model in the index group to test the association between maternal glycemic control in pregnancy (HbA_{1c}) and offspring cognitive function. Offspring test scores were the outcome measure, and HbA_{1c} was included as a continuous exposure variable; the regression coefficient (β) expresses the change in test score corresponding to a 1% increase in HbA_{1c}. Statistical analyses were performed using IBM SPSS Statistics, version 22, with a significance level of 0.05.

RESULTS

A total of 277 (37.1%) diabetes-exposed offspring (index group) with a mean age of 16.6 years, and 301 (15.7%) unexposed offspring (control group) with a mean age of 16.8 years, participated in the follow-up examination of cognitive function (Supplementary Fig. 1). All participants were born in Denmark, and 98.8% were of white European ethnicity. Baseline differences between participants and nonparticipants in the index group were found according to maternal periconceptional HbA_{1c} (first trimester or latest prepregnancy HbA_{1c} in case of missing value) and bwSDS. Participants had a lower maternal HbA_{1c} (7.3% [56 mmol/mol] vs. 7.5% [58 mmol/mol], P = 0.015) and a higher bwSDS (1.8 vs. 1.5, P = 0.016) compared with nonparticipants. Participants and nonparticipants from the index group were similar with respect to parity, maternal prepregnancy age, maternal prepregnancy BMI, duration of diabetes, and HbA_{1c} in the second and third trimester.

Baseline and follow-up characteristics of included offspring are shown in Table 1. Differences between index and control offspring at baseline were found for gestational age, bwSDS, and proportions of neonatal complications, neonatal hypoglycemia, congenital malformations, nulliparity, and pregnancy complications. The groups did not differ with regard to parental educational length.

In the index group the mean maternal diabetes duration at conception was 12.5 (SD 8.3) years. Frequencies of pregestational proliferative retinopathy and macroalbuminuria were 6.9% and 4.7%, respectively.

Intelligence and Memory Indices

Index offspring had lower scores on all cognitive measures compared with the control group: composite intelligence (95.7 vs. 100, P = 0.001), verbal intelligence (96.2 vs. 100, P = 0.004), nonverbal intelligence (96.4 vs. 100, P = 0.008), and composite memory (95.7 vs. 100, P = 0.001) (Table 2). Scores on composite intelligence and composite memory were still lower in the diabetes-exposed offspring after adjustment for known confounders and potential mediators (Table 3).

Furthermore, in the index and control groups combined, age at follow-up (β = 1.23, 95% CI 0.28–2.19, P = 0.01), parental educational length (β = 0.92, 95% CI 0.54–1.30, $P < 0.001$), maternal age at delivery (β = 0.56, 95% CI 0.15–0.96, P = 0.007), and bwSDS (β = 1.19, 95% CI 0.27–2.11, P = 0.01) were independent positive predictors of composite intelligence, while multiparity was an independent negative predictor (β = −4.87, 95% CI −8.23 to −1.50, P = 0.005). Independent positive predictors of composite memory were parental educational length (β = 0.59, 95% CI 0.23–0.95, P = 0.001) and

Table 1—Baseline and follow-up characteristics in adolescent offspring exposed to maternal type 1 diabetes and in an unexposed control group

	*n**	Exposed	Unexposed	*P*
Baseline				
N		277	301	
Male sex (%)	277/301	40.8% (113)	39.9% (120)	0.820
Gestational age at delivery (days)†	260/220	260 (251–266)	280 (273–287)	<0.001
Preterm delivery (<37 weeks)	260/220	41.2% (107)	4.1% (9)	<0.001
Preterm delivery (<34 weeks)	260/220	10.4% (27)	0.5% (1)	<0.001
Birth weight (g)†	263/225	3,680 (3,190–4,090)	3,580 (3,300–3,825)	0.119
bwSDS†	258/220	1.78 (0.38–3.27)	−0.04 (−0.60 to 0.62)	<0.001
Neonatal complications‡	260/198	49.2% (128)	5.1% (10)	<0.001
Neonatal hypoglycemia	265/209	32.5% (86)	0.5% (1)	<0.001
Congenital malformations	265/211	3.8% (10)	0.0% (0)	0.004
Maternal age at delivery (years)	277/301	30.0 (4.1)	29.9 (4.3)	0.783
Nulliparity	266/221	60.2% (160)	42.1% (93)	<0.001
Maternal BMI (kg/m^2)†	223/186	23.0 (21.3–25.2)	22.6 (20.6–24.7)	0.077
Pregnancy complications§	265/190	30.9% (82)	10.5% (20)	<0.001
Follow-up				
Offspring age at follow-up (years)†	277/301	16.6 (15.3–18.0)	16.8 (15.3–18.2)	0.396
Head circumference (cm)	277/301	56.0 (1.76)	56.1 (1.66)	0.495
Parental educational length (years)‖	265/282	27.6 (4.2)	28.2 (4.4)	0.129

Data are mean (SD) or proportion (*n*) unless otherwise indicated. *Exposed/unexposed. Numbers differ between variables because of missing data. †Data are presented as median (interquartile range) when not normally distributed. ‡Hypoglycemia, jaundice, respiratory distress, Apgar 5 <7, systemic infections. §Hydramnios, preeclampsia. ‖Sum of parents' total educational length in years.

maternal age at delivery (β = 0.46, 95% CI 0.07–0.84, *P* = 0.02). Male sex (β = −5.06, 95% CI −8.14 to −1.98, *P* = 0.001) was an independent negative predictor of the composite memory score.

Learning Difficulties

Differences between groups were not found for reading and writing problems in primary school, but index offspring had a higher frequency of learning difficulties in the subjects Danish (23.3 vs. 13.8%) and mathematics (16.4 vs. 7.7%) (Table 2).

Similarly, in crude analyses the ORs for learning difficulties were higher in index offspring compared with control offspring (Table 3). OR for learning difficulties in mathematics remained higher in index offspring after adjustment for confounders and possible mediators. The groups did not differ regarding learning difficulties in Danish after adjustment for confounders (*P* = 0.055) and mediators (*P* = 0.159).

Exposure to maternal diabetes was the only independent positive predictor of learning difficulties in mathematics (OR 2.68, 95% CI 1.09–6.61, *P* = 0.032) but did not predict difficulties in Danish. Independent negative predictors were parental educational level for both mathematics (OR 0.89, 95% CI 0.83–0.97, *P* = 0.005) and Danish (OR 0.90, 95% CI 0.84–0.96, *P* = 0.002) and bwSDS for mathematics (OR 0.79, 95% CI 0.66–0.94, *P* = 0.008).

Table 2—Cognitive function in adolescent offspring of women with type 1 diabetes (*n* = 277) and an unexposed control group (*n* = 301)

	Exposed	Unexposed	*P*
Intelligence indices			
Composite Intelligence Index	95.7 (17.3)	100 (15)	0.001
Verbal Intelligence Index	96.2 (16.8)	100 (15)	0.004
Nonverbal Intelligence Index	96.4 (17.0)	100 (15)	0.008
Composite Memory Index	95.7 (15.3)	100 (15)	0.001
Learning difficulties*			
Reading problems	22.4% (62)	18.7% (56)	0.269
Writing problems	19.3% (52)	16.3% (48)	0.353
Learning difficulties, Danish	23.3% (64)	13.8% (41)	0.003
Learning difficulties, mathematics	16.4% (45)	7.7% (23)	0.001

Data are means (SD) or proportion (*n*). Scores in intelligence and memory indices are based on RIAS. Scores in intelligence and memory indices in the control group were standardized to a mean (SD) of 100 (15). *Parent-reported by questionnaire (by parents or parents and offspring together).

Maternal Glycemic Control

Analysis was restricted to the index group, since HbA_{1c} measurements were limited to women with diabetes in pregnancy. Numbers of measurements pregestational (*n* = 233) and in first (*n* = 252), second (*n* = 259), and third (*n* = 252) trimester varied because of missing data. There were no associations between maternal HbA_{1c} measurements and intelligence or memory indices in crude or adjusted analysis (Supplementary Table 1).

Offspring of women with episodes of severe hypoglycemia in pregnancy (*n* = 32) had lower, although not statistically significant, scores on all intelligence indices compared with diabetes-exposed offspring without hypoglycemic episodes (Table 4).

In line with this, maternal episodes of ketoacidosis (*n* = 5) were associated with markedly lower offspring scores in all intelligence and memory indices (Table 4). Scores in composite intelligence (81.6 vs. 95.5, *P* = 0.078) and composite memory (81.6 vs. 96.0, *P* = 0.035) were >1 SD below the mean of the background population. Because of the limited number of women with severe hypoglycemic and ketoacidotic episodes, adjustments for

Table 3—Regression analysis on Composite Intelligence Index and Composite Memory Index scores and learning difficulties in primary school in offspring of women with type 1 diabetes (*n* = 277) compared with an unexposed control group (*n* = 301)

	Composite Intelligence Index		
Model	β	95% CI	*P*
Crude	−4.35	(−6.99 to −1.71)	0.001
1	−4.12	(−6.97 to −1.27)	0.005
2	−7.60	(−12.11 to −3.09)	0.001
	Composite Memory Index		
Model	β	95% CI	*P*
Crude	−4.30	(−6.78 to −1.82)	0.001
1	−3.73	(−6.52 to −0.95)	0.009
2	−4.97	(−9.27 to −0.67)	0.024
	Learning difficulties, Danish*		
Model	OR	95% CI	*P*
Crude	1.90	(1.23 to 2.93)	0.004
1	1.64	(0.99 to 2.72)	0.055
2	1.78	(0.80 to 3.98)	0.159
	Learning difficulties, Mathematics*		
Model	OR	95% CI	*P*
Crude	2.34	(1.37 to 3.98)	0.002
1	2.26	(1.20 to 4.26)	0.012
2	2.68	(1.09 to 6.61)	0.032

The regression coefficient (β) is the mean difference between the exposed offspring and the control group. Scores in intelligence and memory indices are based on RIAS. Model 1: adjustment for confounders (offspring sex, age at follow-up, parity, parental educational length, maternal age at delivery). Model 2: adjustment for model 1 confounders plus adjustment for potential mediators (neonatal complications, pregnancy complications, gestational age, bwSDS). *Parent reported by questionnaire (by parents or parents and offspring together).

confounders and mediators were not performed.

CONCLUSIONS

In this large nationwide cohort of adolescent offspring we found that those exposed to maternal diabetes had impaired cognitive function compared with a control group. Differences between groups could not be explained by confounders or mediators, indicating a harmful effect of intrauterine hyperglycemia. However, we were not able to demonstrate any direct association between maternal HbA_{1c} in pregnancy and cognitive performance in the offspring.

Table 4—Association between maternal episodes of severe hypoglycemia or ketoacidosis in pregnancy and offspring scores in RIAS in offspring of women with type 1 diabetes

	Present	Not present	*P*
Severe hypoglycemia in pregnancy	32	221	
Composite Intelligence Index	89.7 (19.0)	95.9 (17.0)	0.06
Verbal Intelligence Index	90.8 (18.8)	96.5 (16.7)	0.07
Nonverbal Intelligence Index	91.5 (18.6)	96.6 (16.7)	0.110
Composite Memory Index	93.4 (17.1)	95.9 (14.9)	0.381
Model	5	249	
Composite Intelligence Index	81.6 (19.5)	95.5 (17.3)	0.078
Verbal Intelligence Index	82.3 (12.7)	96.0 (16.9)	0.073
Nonverbal Intelligence Index	85.8 (26.2)	96.4 (17.0)	0.172
Composite Memory Index	81.6 (17.0)	96.0 (15.1)	0.035

Data are presented as *n* or mean (SD). Numbers differ between variables because of missing data.

An apparent limitation is the risk of selection bias because of the low participation rate (index 37.1% and control subjects 15.7%).

Previous studies, using various assessments of cognitive function, have reported lower cognitive performance in offspring exposed to maternal diabetes (18,20,24) but, in most cases, with limitations due to either study size or lack of differentiation between diabetes types. The inclusion of offspring in our study was restricted to offspring of women with type 1 diabetes. It is a strength, since different diabetes types may have diverse metabolic presentations in pregnancy.

In a study of adult offspring of Danish women with type 1 diabetes, differences in intelligence scores between diabetes-exposed offspring and control subjects were similar, as suggested in our study, with many shared independent predictors of offspring cognitive function (17). However, Clausen et al. (17) found no association between exposure and cognitive function after adjustment for known confounders, which might reflect the smaller study population (diabetes-exposed offspring *n* = 158) compared with our cohort (diabetes-exposed offspring *n* = 277).

Adjustment for confounders and mediators in our study did not change the association between intrauterine diabetes exposure and offspring cognitive function. Thus, our results imply a direct influence of intrauterine hyperglycemia on offspring cognitive function not accounted for by known confounders or potential mediators.

We showed differences between the diabetes-exposed and -unexposed groups in terms of learning difficulties in primary school. Information about learning difficulties was parent-reported, and some inaccuracy is potentially associated with this variable. We were not able to validate this information with information from other sources. Learning difficulties are often associated with other cognitive impairments, and it would be interesting to ascertain the frequency of attention deficit disorders and other aberrant neurodevelopment in the offspring. Recently, autism spectrum disorders have been suggested to be associated with maternal gestational diabetes mellitus (30).

Our group has previously shown that diabetes-exposed offspring and a control

group had similar school achievement in primary school in a register study based on the EPICOM population (19). However, there was an inverse association between maternal glycemic control and offspring school grades, which may reflect advanced maternal executive skills related to management of a complex chronic disease. The discrepancy between findings in the register-based study and the current study could be explained by greater measurement precision and sensitivity of intelligence tests compared with school grades. However, it is reassuring that the offspring attain school grades in primary school similar to those of unexposed offspring despite lower cognitive function. This difference may theoretically be explained by the larger proportion of diabetes-exposed offspring attending classes for children with learning problems in primary school observed in our study, which may help students attain higher school grades. Finally, the discrepancy between findings could be a result of sample bias, since only a third of the invited population participated in the current study. A future study of the highest attained educational level in adult offspring would be valuable to evaluate whether diabetes-exposed offspring are able to compensate for the lower cognitive function after primary school.

A few recent studies report findings of a positive effect of a diabetic intrauterine environment on offspring cognitive function (21,25,26), all with limited statistical power. A study, using Swedish register data to evaluate cognitive performance in male siblings discordant for exposure to maternal diabetes, found diabetes in pregnancy associated with lower academic achievement at age 16 years and lower intelligence quotient at conscription in nonsiblings but not in siblings discordant for maternal diabetes exposure (25). The association between maternal diabetes and intelligence quotient at conscription within siblings was positive but small and nonsignificant.

Bonilla et al. (26) applied a Mendelian randomization strategy and identified a discrete positive association between maternal genetic risk scores for type 2 diabetes and offspring intelligence at 8 years of age. The authors suggest the possibility of beneficial effects of increased glucose flow related to risk genes to the child's intrauterine neurological development, shifting to an adverse effect after establishment of a clinical diabetic disease.

Maternal Glycemic Control

Recommendations of glycemic control in the 1990s, when the register of pregnant women with type 1 diabetes was established, allowed higher levels of HbA_{1c} than current guidelines. An HbA_{1c} level in pregnancy $<$7% (53 mmol/mol) was considered acceptable; thus, HbA_{1c} levels in our cohort were higher than we would expect today (31). In a Danish study using cognitive scores at conscription, HbA_{1c} was negatively associated with offspring cognitive function, but when HbA_{1c} levels were $<$7% (53 mmol/mol) cognitive function was the same as in control subjects (23). Mean maternal HbA_{1c} in our cohort was $>$7% pregestational and in first trimester.

However, we were not able to find any association between maternal HbA_{1c} levels and test scores in the index offspring, which may indicate that additional factors other than glucose are responsible in the link between intrauterine hyperglycemia and offspring cognitive function.

The validity of HbA_{1c} as measurement of overall glycemic control in pregnancy could be another explanation. HbA_{1c} measurements reflect the mean glycemic level but with more impact of the recent glucose levels (32). The glucose levels change physiologically during pregnancy, resulting in different physiological levels dependent on the timing of the measurement in each trimester. Furthermore, HbA_{1c} does not reflect the stability of the glucose level, and fluctuating glucose levels may be more harmful than a constant high level. Continuous glucose monitoring in pregnancy would be valuable in this context, since it would address these issues. Our analysis of maternal episodes of hypoglycemia and ketoacidosis and offspring cognitive function could support this, even though statistical power is limited. Offspring of women with episodes of ketoacidosis obtained very low scores both compared with offspring without maternal ketoacidosis and compared with the normal population mean. Our inability to adjust for confounders is important in this context because educational level and family resources are important confounders in this association. We still think this finding is noteworthy, and special attention to these children should be considered.

Strengths and Limitations

The major strength to our study was the use of a large well-characterized prospectively followed cohort of women with type 1 diabetes. We had detailed baseline information, enabling us to adjust for multiple confounders and possible mediators in the pathway between maternal diabetes and offspring cognitive function. Unfortunately, we did not have sufficient information about delivery mode, breast-feeding, and maternal smoking in pregnancy to include these variables with possible implications on offspring cognitive function (33). Diverse effects of breast-feeding on cognitive development in offspring of women with diabetes have previously been suggested (34,35).

A limitation is the risk of selection bias, since a limited and different proportion of invited offspring in the two groups agreed to participate at follow-up. This might lead to selection bias if nonparticipation is related to cognitive function. Participation may be associated with parental concern about the child's cognitive function, but nonparticipation is in general associated with lower socioeconomic status, educational level, and health status (36). Cognitive results before standardization and normalization show mean scores in all variables $>$100 in both groups (data not shown). A mean of 100 is the population mean in intelligence tests and implies that both groups were selected from the better-performing part of the population. Offspring of women with ketoacidosis or hypoglycemia tended to perform worse than offspring of women without these complications, and their participation rate was lower than that for the entire diabetes-exposed group (28% vs. 37%), implying no selection of children with lower performance in the exposed group. The cognitive tests were a minor part of a comprehensive examination plan (9). None of the offspring chose to confine their participation to the cognitive tests, so we do not consider these tests as the primary motivation for participation in either of the groups.

Chronic diseases among the offspring could potentially affect cognitive function, but we did not have sufficient

information to include this in our analyses. Unfortunately, we were not allowed to collect information regarding baseline information in nonparticipants in the control group. In the index group, analysis showed comparability at birth between participants and nonparticipants. There was a slightly better periconceptional HbA_{1c} in the group of mothers with participating index offspring, which probably reflect a higher frequency of pregnancy planning and better glucose control prior to pregnancy. These women tend to have more resources in many aspects of life, and their offspring are not expected to be in the group with the lower cognitive function. An underestimation of the association with exposure is therefore more likely than the opposite. A lower HbA_{1c} could reflect more frequent events of hypoglycemia, but we did not find any difference in hypoglycemic events in early pregnancy between participating and nonparticipating mothers.

We did not have information about maternal or paternal intelligence and were unable to adjust for effects of genetic factors and family environment on offspring cognitive function. Educational achievement and intelligence are considered to be closely related (37,38), and parental educational level is a well-known predictor of offspring cognitive function. Complete adjustment for parental genetic and socioeconomic contribution is difficult, and incomplete adjustment for these factors is the most obvious contributor to residual confounding in our analysis. Individuals with a chronic disease tend to attain a lower educational level compared with those without disease (39), possibly resulting in underadjustment of the genetic contribution in the index group and an underestimation of the association between exposure and outcome—minimized, though, by the inclusion of the paternal educational level.

The missing baseline data in the control group caused by inability to obtain obstetric records could have implications on adjusted analysis. The need for adjustment for multiple comparisons in Table 2 and 3 could be discussed. We considered Bonferroni correction to be too conservative, since outcomes in both tables are closely related and not independent. However, both unadjusted and most adjusted differences between groups would still be present after Bonferroni correction (data not shown).

In conclusion, results from this well-characterized prospectively followed cohort indicate harmful effects of maternal diabetes on neurodevelopment in the offspring of mothers with type 1 diabetes. Exposure to maternal diabetes had an effect on all intelligence indices, and cues to specific brain areas affected were not obvious in our study. Increased attention to the group of children at special risk of cognitive impairment, who could benefit from early intervention on cognitive difficulties, is necessary. Future studies may be able to evaluate implications of maternal glycemic control in pregnancy using a more precise glycemic measurement.

Acknowledgments. Data collection in the original registry was performed by Lars Mølsted-Pedersen, Joachim Klebe, Niels Hahnemann, Margrethe Møller, Jes G. Westergaard, Hans Gjessing, Jens Kragh Mostrup, K.H. Frandsen, Edna Stage, Anders Thomsen, Thea Lousen, Kresten Rubeck Petersen, Bjarne Øvlisen, Jan Kvetny, and Hedvig Poulsen. Apart from H.B.-N. and P.D., the original registry working group included Anders Frøland, Lars Mølsted-Pedersen, Joachim Klebe, and Carl Erik Mogensen.

Funding. The study was supported by the European Foundation for the Study of Diabetes, Danish Ministry of Science, Innovation and Higher Education, Lundbeck Foundation, Danish Diabetes Academy, Beckett Foundation, and Danielsen Foundation.

The sponsors of the study had no involvement in design, conduct, or interpretation of the study.

Author Contributions. B.B., S.K., and Z.V. performed the data collection. B.B., S.K., Z.V., R.B.J., E.R.M., H.B.-N., C.H.G., D.M.J., T.D.C., E.L.M., and P.D. contributed substantially to the conception and design of the study. B.B., R.B.J., T.D.C., E.L.M., and P.D. analyzed data. B.B. drafted the manuscript and designed the tables. H.B.-N., D.M.J., and P.D. have contributed to the establishment of the original register. All authors were involved in the interpretation of data, critically revised the article, and approved the final version. B.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Duality of Interest. R.B.J., H.B.-N., C.H.G., and P.D. have given talks for Novo Nordisk (NN). D.M.J. has given talks for Eli Lilly. H.B.-N. receives research support from NN. E.R.M. and P.D. are participating in a multinational study in collaboration with NN. No other potential conflicts of interest relevant to this article were reported.

Prior Presentation. Parts of this study were presented in abstract form at the 47th Annual Meeting of the Diabetes in Pregnancy Study Group, 1–4 October 2015, Malaga, Spain.

References

1. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004;27:2819–2823
2. Knorr S, Stochholm K, Vlachová Z, et al. Multisystem morbidity and mortality in offspring of women with type 1 diabetes (the EPICOM study): a register-based prospective cohort study. Diabetes Care 2015;38:821–826
3. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177
4. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004;328:915
5. Clausen TD, Mathiesen ER, Hansen T, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. J Clin Endocrinol Metab 2009;94:2464–2470
6. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and prediabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. Diabetes Care 2008;31:340–346
7. Sobngwi E, Boudou P, Mauvais-Jarvis F, et al. Effect of a diabetic environment in utero on predisposition to type 2 diabetes. Lancet 2003; 361:1861–1865
8. Fraser A, Lawlor DA. Long-term health outcomes in offspring born to women with diabetes in pregnancy. Curr Diab Rep 2014;14:489
9. Vlachová Z, Bytoft B, Knorr S, et al. Increased metabolic risk in adolescent offspring of mothers with type 1 diabetes: the EPICOM study. Diabetologia 2015;58:1454–1463
10. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev 2010;20:327–348
11. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. Front Neurosci 2015;9:194
12. Sullivan EL, Nousen EK, Chamlou KA, Grove KL. The impact of maternal high-fat diet consumption on neural development and behavior of offspring. Int J Obes Suppl 2012;2:S7–S13
13. Xu G, Jing J, Bowers K, Liu B, Bao W. Maternal diabetes and the risk of autism spectrum disorders in the offspring: a systematic review and meta-analysis. J Autism Dev Disord 2014;44:766–775
14. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatry 2001;58:1032–1037
15. Brown AS, van Os J, Driessens C, Hoek HW, Susser ES. Further evidence of relation between prenatal famine and major affective disorder. Am J Psychiatry 2000;157:190–195
16. Li Y, Gonzalez P, Zhang L. Fetal stress and programming of hypoxic/ischemic-sensitive phenotype in the neonatal brain: mechanisms and possible interventions. Prog Neurobiol 2012;98:145–165
17. Clausen TD, Mortensen EL, Schmidt L, et al. Cognitive function in adult offspring of women with type 1 diabetes. Diabet Med 2011;28:838–844
18. Dahlquist G, Källén B. School marks for Swedish children whose mothers had diabetes

during pregnancy: a population-based study. Diabetologia 2007;50:1826–1831
19. Knorr S, Clausen TD, Vlachová Z, et al. Academic achievement in primary school in offspring born to mothers with type 1 diabetes (the EPICOM study): a register-based prospective cohort study. Diabetes Care 2015;38:1238–1244
20. Silverman BL, Rizzo TA, Cho NH, Metzger BE; The Northwestern University Diabetes in Pregnancy Center. Long-term effects of the intrauterine environment. Diabetes Care 1998; 21(Suppl. 2):B142–B149
21. Veena SR, Krishnaveni GV, Srinivasan K, et al. Childhood cognitive ability: relationship to gestational diabetes mellitus in India. Diabetologia 2010;53:2134–2138
22. Temple RC, Hardiman M, Pellegrini M, Horrocks L, Martinez-Cengotitabengoa MT. Cognitive function in 6- to 12-year-old offspring of women with Type 1 diabetes. Diabet Med 2011;28:845–848
23. Nielsen GL, Dethlefsen C, Sørensen HT, Pedersen JF, Molsted-Pedersen L. Cognitive function and army rejection rate in young adult male offspring of women with diabetes: a Danish population-based cohort study. Diabetes Care 2007;30:2827–2831
24. Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Exp Diabetes Res 2012;2012:963735
25. Fraser A, Almqvist C, Larsson H, Långström N, Lawlor DA. Maternal diabetes in pregnancy and offspring cognitive ability: sibling study with 723,775 men from 579,857 families. Diabetologia 2014;57:102–109
26. Bonilla C, Lawlor DA, Ben-Shlomo Y, et al. Maternal and offspring fasting glucose and type 2 diabetes-associated genetic variants and cognitive function at age 8: a Mendelian randomization study in the Avon Longitudinal Study of Parents and Children. BMC Med Genet 2012;13:90
27. Smith BL, McChristian CL, Smith TD, Meaux J. The relationship of the Reynolds Intellectual Assessment Scales and the Wechsler Adult Intelligence Scale-Third Edition. Percept Mot Skills 2009;109:30–40
28. Allen DN, Stolberg PC, Thaler NS, Sutton G, Mayfield J. Validity of the RIAS for assessing children with traumatic brain injury: sensitivity to TBI and comparability to the WISC-III and WISC-IV. Appl Neuropsychol Child 2014; 3:83–93
29. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843–848
30. Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. JAMA 2015;313:1425–1434
31. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care 2013;36:1877–1883
32. Saudek CD, Brick JC. The clinical use of hemoglobin A1c. J Diabetes Sci Technol 2009;3:629–634
33. Rahu K, Rahu M, Pullmann H, Allik J. Effect of birth weight, maternal education and prenatal smoking on offspring intelligence at school age. Early Hum Dev 2010;86:493–497
34. Plagemann A, Harder T, Kohlhoff R, et al. Impact of early neonatal breast-feeding on psychomotor and neuropsychological development in children of diabetic mothers. Diabetes Care 2005;28:573–578
35. Rodekamp E, Harder T, Kohlhoff R, Dudenhausen JW, Plagemann A. Impact of breast-feeding on psychomotor and neuropsychological development in children of diabetic mothers: role of the late neonatal period. J Perinat Med 2006;34:490–496
36. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17:643–653
37. Deary IJ, Strand S, Smith P, Fernandes C. Intelligence and educational achievement. Intelligence 2007;35:13–21
38. Deary IJ, Johnson W. Intelligence and education: causal perceptions drive analytic processes and therefore conclusions. Int J Epidemiol 2010;39:1362–1369
39. Champaloux SW, Young DR. Childhood chronic health conditions and educational attainment: a social ecological approach. J Adolesc Health 2015;56:98–105